THE AMERICAN SURGEON

Vol. 24, No. 9 September, 1958

TRANSECTION OF THE HYPOPHYSEAL STALK IN THE MANAGEMENT OF METASTATIC MAMMARY CARCINOMA*

GORDON S. DUGGER, M.D., JUDSON VAN WYKE, M.D., AND JAMES F. NEWSOME, M.D.

Chapel Hill, North Carolina

Distant spread of carcinoma of the breast will occur in a majority of women regardless of the type of treatment given to the primary lesion. The rate of growth of metastatic mammary carcinoma is highly variable. In some patients growth is rapid but in many others metastases do not become evident until years after the primary lesion has been ablated. Whether the rate of growth of the tumor is rapid or slow, palliative treatment has an important part in the management of this disease.

For many years it has been known that hormonal factors are important in the production and growth of carcinoma of the breast. Beatson,[1] in 1896, reported a remission of the disease after oophorectomy. In 1919 Loeb[7] pointed out that in the experimental animal carcinoma of the breast was produced by two factors. The first factor he called heredity and the second, stimulus. Because the stimulating or promoting factor in carcinoma of the breast probably is estrogen, it is inevitable that attempts would be made to modify the course of the disease by altering the hormone environment. This has been done in a variety of ways, and endocrine treatment does afford effective palliation for many patients with mammary carcinoma.

Improvement in some patients with carcinoma of the breast has been observed while they are given androgens or cortisone.[10] Oophorectomy induced objective remissions in 44 per cent of premenopausal women with metastatic mammary carcinoma, and bilateral removal of the adrenals provided effective palliation in 45 per cent.[10] Apparently the effectiveness of both of these procedures is a result of the removal of the sources of endogenous estrogens.[11]

In 1953 Luft and Olivecrona[8] reported their experiences with hypophysectomy in man for certain malignant neoplasms, insulin resistant diabetes mellitus, Cushing's syndrome and malignant hypertension. Later these authors[9] indicated that of 37 patients with metastatic carcinoma of the breast 30 could be evaluated, and 50 per cent improved after hypophysectomy. Ray and Pearson[14] found that 36 out of 74 patients with metastatic breast carcinoma showed objective remission of their disease for varying periods of time, after hypophysectomy.

Recognizing that total hypophysectomy is often difficult to perform and that total removal of the gland is not achieved always, we have attempted to cause a functional hypophysectomy by interfering with the mechanism responsible for the activity of the gland. The mechanism for the neural regulation of the hypophysis still is not decided. Recent accounts[12] describe few nerve fibers in the adenohypophysis. Moreover, transection of the hypophyseal stalk separates completely and permanently the gland from any direct nervous control from the hypothalamus because the hypothalamic-hypophyseal tracts cannot regenerate. Although the results are somewhat divergent, it seems that hypophyseal stalk transection *per se* does not interfere with the function of the adenohypophysis.[4] In only a few instances has transection of the hypophyseal stalk in man been reported. Dandy[2] sectioned the stalk in a young woman who afterwards had normal menstrual periods and ultimately became preg-

* From the Department of Surgery, Division of Neurosurgery, and Department of Pediatrics of the School of Medicine of the University of North Carolina, and the North Carolina Memorial Hospital, Chapel Hill, N. C.

nant. Rasmussen and Gardner[13] sectioned the stalk in a patient who lived for five months, but the case report did not mention any endocrine disturbance.

Harris[5] and Green and Harris[3] suggested that nervous stimuli liberated some substance into the capillaries of the median eminence which passed down the hypophyseal portal vessel system either to stimulate or inhibit the adenohypophysis. Harris[6] showed that after section of the hypophyseal stalk in rats the portal vessels regenerated with facility, and there was a good correlation between this vascular regeneration and the return of reproductive function. However, if after stalk transection some impervious material was placed between the cut ends, the adenohypophysis was not revascularized by the hypophyseal portal vessels and the animals remained anestrous.

Based upon the above experimental evidence the procedure used to cause a functional hypophysectomy consisted of transection of the infundibular stem or hypophyseal stalk and the placement of a disc of impervious material across the sella turcica. Thus the revascularization of the hypophysis by vessels from the hypothalamus, specifically the vessels of the hypophyseal portal system, became unlikely. Beginning in July 1955 this operation has been done in a small series of 15 patients with advanced metastatic carcinoma of the breast. Endocrine function was assayed in all patients preoperatively and in the patients who survived sufficiently long postoperatively. Studies were made of the uptake of I-131, protein-bound iodine (PBI), excretion of gonadotropins, 17-ketosteroids and 17-hydroxycorticosteroids and response of plasma 17-hydroxycorticosteroids to the adrenocorticotropic hormone (ACTH). The I-131 uptake and the PBI were reduced in the patients who had normal tests before operation. Low titers of follicle-stimulating hormone (FSH) could be assayed in patients postoperatively, but high initial titers were unusual in this group. In all patients after operation the excretion of 17-ketosteroids and 17-hydroxycorticosteroids was diminished to very low levels. The detailed endocrine effects of the procedure are to be reported at another time.

INDICATIONS FOR HYPOPHYSEAL STALK TRANSECTION

The patients selected for operation had far advanced metastatic mammary carcinoma. Either other reasonable means of palliation had failed or the effects had terminated.

Palpable or visible metastatic lesions, radiologically identifiable metastases to bones and pleural effusions containing neoplastic cells were accepted as evidence of dissemination. Some patients were operated upon who now, in the light of our experience with the procedure, would be excluded. These were patients whose condition was truly hopeless because of global spread of disease. Also, patients with metastases to the liver should not be operated upon. Patients with recognizable intracranial metastases were excluded from the beginning as were those with serious impairment of respiratory function from intrapulmonary metastases.

THE OPERATION AND HORMONAL REPLACEMENT

Only a brief description of the operative method will be given. General endotracheal anesthesia was used. The patients were postured in the supine position often with the head dropped back and rotated slightly away from the side of the incision. A right frontal osteoplastic craniotomy with a free bone plate was made. While the dura was being opened, cerebrospinal fluid was allowed to escape from a catheter placed in the lumbar subarachnoid space. This was extremely important because in the one instance in which the catheter did not function exposure was difficult; whereas, with the loss of fluid only minimal light retraction of the frontal lobe was required to visualize the optic nerves and chiasm. At first the approach was near the midline along the falx but this exposed to tearing the veins that commonly run into the saggital sinus, an occurrence that may lead to a red infarction of the frontal lobe. Later the approach to the sellar region was made just anterior to the lesser wing of the sphenoid and this afforded satisfactory visualization of the hypophyseal stalk. The stalk was sharply divided as low as possible. At first it was coagulated or compressed with a clip but this increased the liability to and the severity of diabetes insipidus. The bleeding from the cut stalk was trivial. A disc of impervious material was then placed across the sella turcica between the cut ends of the stalk. The disc that was used has always been tantalum but other materials would perhaps serve as well. If the optic nerves had been short, recourse to some pliable material might have been necessary. Aside from the routine of the craniotomy and its closure the procedure required about 15 minutes.

During the operation the patients were given 100 mg. of hydrocortisone intravenously and 100 mg. of cortisone after the operation. For a few days after operation they took by mouth 15 mg. of prednisone a day in divided doses. The amount of prednisone was reduced gradually and then eliminated before tests of hypophyseal function were carried out.

POSTOPERATIVE MORTALITY

The operative mortality should be an expression of the deaths caused primarily by the operative procedure. This was difficult to evaluate because for the most part the operation was done on patients who were already seriously ill. All of the patients who died within some arbitrary period of time after operation were not considered as operative deaths because some of the patients who survived only a short time after operation died as a result of the advanced degree of their disease. One patient survived the operation only one day and her death was caused directly by the operation which was done even though she had a serious reduction in vital capacity from extensive intrapulmonary metastases. Another patient who survived only nine days, at autopsy was found to have global dissemination of carcinoma and death could be attributed to this rather than to the operation. A patient who survived 25 days seemed to have died because of the advance of her disease and this appeared to be true of the other patients in the series who have died. The time of survival after operation is given in table 1.

POSTOPERATIVE MORBIDITY

The postoperative morbidity is easier to evaluate than mortality. Most of the patients did well and were able to get out of bed on the second day after operation. The serious neurologic complications were visual field defects, oculomotor nerve palsy and focal cerebral seizures. The most common complication was focal cerebral motor seizures which occurred in 5 patients or 30 per cent of the cases, but they did not occur in the last 6 patients. They appeared on the first or second postoperative day and usually were limited to the face. In one patient they became generalized with loss of consciousness. None of the 5 patients has had seizures after the early postoperative period although anticonvulsant medication was not given past this time.

The visual field defect was an incomplete bitemporal hemianopsia with preservation of useful vision. This was a complication in the first patient operated upon and she had short optic nerves, requiring elevation of the optic chiasm to place the tantalum disc. The occulomotor palsy occurred on the second day after operation and was difficult to explain unless the tantalum disc was shifted against the nerve by brain edema or a small hematoma. Considerable recovery of the levator palpebrae superioris was evident 10 days later but troublesome diplopia persisted. There were no postoperative intracranial clots. None of the patients complained of loss of smell although the right olfactory nerve was divided deliberately.

TABLE 1

Length of survival after operation

1. L. W.	52 days
2. M. K.	4 months
3. M. G.	9 months
4. D. S.	1 day
5. S. Mc.	53 days
6. D. L.	16 months*
7. E. B.	9 days
8. K. P.	13 months*
9. E. L.	8 months
10. M. P.	4 months
11. N. C.	25 days
12. H. N.	2 months*
13. K. S.	1 month*
14. A. H.	1 month*
15. A. P.	1 month*

* Indicates patient is alive.

TABLE 2

Results of operation

Remission		6
Arrest	3	
Regression	3	
No benefit		4
Operative death		1
Too early to evaluate		4
Total		15

RESULTS

The favorable results from the operation could be divided into two groups. The first group consisted of the patients who showed a regression of their disease. Regression was determined by a decrease in size of palpable or visible lesions, disappearance of intrapulmonary metastases or pleural effusions and the healing of osseous metastases, the latter determined by x-ray exami-

TABLE 3

Duration of remission

	mo.
M. K.	3
M. G.	8
D. L.	6
K. P.	12
E. L.	7
M. P.	4
Average duration of remission	6.6 mos.

TABLE 4

Results according to endocrine status

Premenopausal		4
Arrest	0	
Regression	1	
No benefit	2	
Not evaluated	1	
Postmenopausal		11
Arrest	3	
Regression	2	
No benefit	2	
Not evaluated	4	

nation. The second group consisted of patients who showed arrest of their disease. Arrest was determined by a halt in the growth of previously progressive lesions and the absence of new lesions in patients in whom new lesions had been appearing rapidly. Table 2 shows the results according to the above criteria. Six patients had some remission of their disease but three showed arrest and three regression. Four patients received no benefit from operation and four were too early to evaluate. Figure 1 shows the resolution of a pleural effusion in one patient and figure 2 the disappearance of intrapulmonary and the healing of osseous metastases in another.

Table 3 shows the duration of remission in 6 patients. This averaged 6.6 months but the spread was from 3 months to 12 months. The patient whose remission lasted 12 months is alive but now she has new lesions.

Most of the patients operated upon were postmenopausal. Table 4 lists the results according to the patient's endocrine status and indicates that a remission can occur in both groups.

The subjective effects of the procedure have not been tabulated, but the relief of pain after operation often has been dramatic.

DISCUSSION

The results of this procedure ultimately must be compared with the results achieved by total hypophysectomy. However, the clinical course of mammary carcinoma is so variable that a small series of 15 patients is not statistically significant. Furthermore, because of the experimental nature of the procedure the operation was used on patients with far advanced disease. It may well be that in some of these patients the great majority of the neoplastic cells had gained

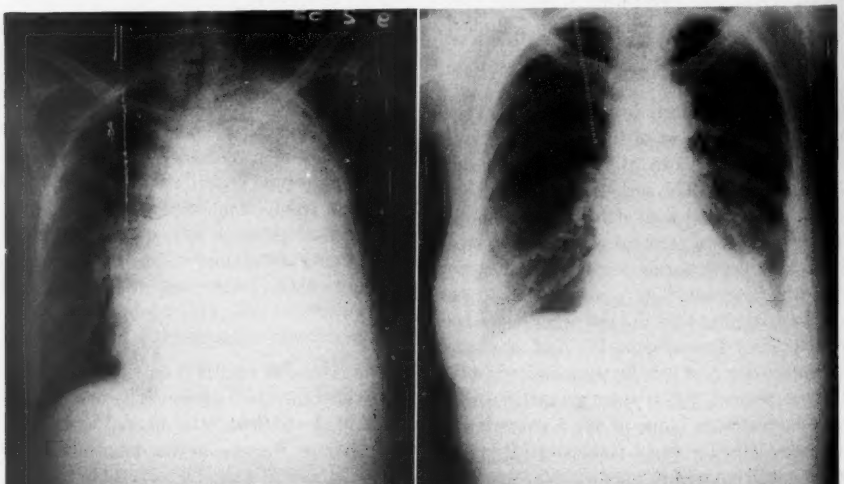

FIG. 1. Resolution of a pleural effusion following transection of the hypophyseal stalk.

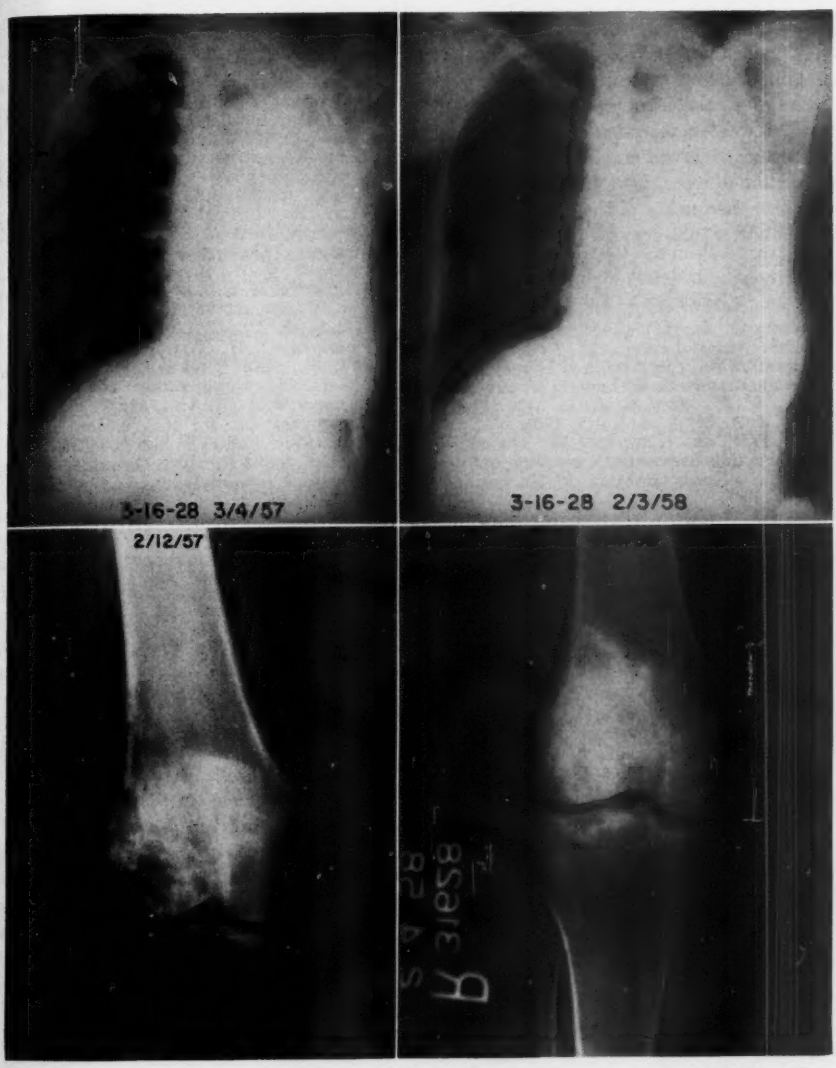

FIG. 2. Disappearance of intrapulmonary metastasis indicated by arrow and the healing of osseous metastases around the knee after transection of the hypophyseal stalk.

autonomy from the stimulating factor. Certainly some of the early cases, particularly those with liver metastases, now would be excluded from operation. Because of this fact and the smallness of the series the average survival time of 5.1 months for all patients and the average duration of remission of 6.6 months for those patients surviving the procedure probably did not mean a great deal. Even so the average duration of remission was not so long as that reported by others after total hypophysectomy.[14] Whether the remissions we have observed after hypophyseal stalk transection are qualitatively the same as those obtained with total hypophysectomy has not been determined.

CONCLUSIONS

1. After transection of the hypophyseal stalk in a series of 15 patients with far advanced

metastatic mammary carcinoma 6 showed a remission, 4 gained no benefit, one died as a result of operation, and 4 are too early to evaluate.

2. Average duration of remission was 6.6 months. This was less than that reported for total hypophysectomy but will probably improve with better selection of cases.

3. Whether the quality of the remission is the same as that after total hypophysectomy has not been determined.

REFERENCES

1. Beatson, G. T.: On the treatment of inoperable cases of carcinoma of the mamma: Suggestion for a new method of treatment, with illustrative cases. Lancet, *11:* 104, 1896.
2. Dandy, W. E.: Section of the hypophyseal stalk. J. A. M. A., *114:* 213, 1940.
3. Green, J. D., and Harris, G. W.: The neurovascular link between the neurohypophysis and the adenohypophysis. J. Endocrinol., *5:* 136, 1947.
4. Harris, G. W.: Neural control of the pituitary gland. Physiol. Rev., *28:* 139, 1948.
5. Harris, G. W.: The hypothalamus and endocrine glands. Brit. M. Bull., *6:* 345, 1950.
6. Harris, G. W.: Oestrous rhythm. Pseudopregnancy and pituitary stalk in rat. J. Physiol., *111:* 347, 1950.
7. Loeb, L.: Further investigations on the origin of tumor in mice. VI. Internal secretion as a factor in the origin of tumors. J. Med. Res., *40:* 477, 1919.
8. Luft, R., and Olivecrona, H.: Experiences with hypophysectomy in man. J. Neurosurg., *10:* 301, 1953.
9. Luft, R., and Olivecrona, H.: Hypophysectomy in man: Experiences in metastatic cancer of the breast. Cancer, *8:* 261, 1955.
10. Pearson, O. H., Li, M. C., MacLean, J. P., Lipsett, M. B., and West, C. D.: Management of metastatic mammary cancer. J. A. M. A., *159:* 1701, 1955.
11. Pearson, O. H., West, C. D., Hollander, V. P., and Treves, N.: Evaluation of endocrine therapy for advanced breast cancer. J. A. M. A., *154:* 234, 1954.
12. Rasmussen, A. T.: Innervation of the hypophysis. Endocrinology, *23:* 263, 1938.
13. Rasmussen, A. T., and Gardner, W. J.: Effects of hypophyseal stalk resection on the hypophysis and hypothalamus of man. Endocrinology, *27:* 219, 1940.
14. Ray, B. S., and Pearson, O. H.: Hypophysectomy in the treatment of advanced cancer of breast. Ann. Surg., *144:* 394, 1956.

SOME CONSIDERATIONS CONCERNING PNEUMONECTOMY IN THE TREATMENT OF PULMONARY TUBERCULOSIS

ROBERT ZEPPA* AND RICHARD M. PETERS

Chapel Hill, North Carolina

In general, the criteria for the resection therapy of pulmonary tuberculosis include the removal of cavities and fibrocaseous foci of certain specified size in expectation of achieving sputum conversion and a reduced incidence of disease reactivation. In the patient's terms, these imply discharge from the sanatorium, return to gainful employment and the resumption of a normal life. Surgical therapy is also required in the treatment of such consequences of tuberculous infection as bronchiectasis, bronchostenosis and fibrothorax, which of themselves may be as crippling as the disease proper.

The newer developments in antibiotic therapy, anesthesia, blood replacement and surgical technique have contributed to an increase in the safety associated with surgical therapy. The mortality following lobectomy has decreased from 26 per cent in 1942[12] to almost 1 per cent in 1957.[1] During this same interval of time, the mortality resulting from pneumonectomy has decreased only threefold, from 45 per cent to 14 per cent.[3, 12] This procedure is still attended by a serious risk to life. Complications such as bronchopleural fistula and empyema are sometimes fatal to the patient. Frequently, complete extirpation of the tuberculous process is not accomplished. These facts are readily available from examination of past and recent reports concerned with this form of therapy.[4, 6, 9, 11] Consequently, the justification for this harsh therapeutic regimen should be examined closely as should all aspects of the pre- and postoperative care.

This report presents the considerations concerning the care of tubercular patients in whom a pneumonectomy is indicated. Particular emphasis will be placed on the indications for this radical form of therapy and how the morbidity and mortality can be reduced.

MATERIAL AND RESULTS

During the period 1953 to 1957, 37 patients from Gravely Sanatorium, Chapel Hill, North Carolina, underwent pneumonectomy for tuberculosis at the North Carolina Memorial Hospital. The details to be discussed are present in tabular form in tables 1 and 2. The ages ranged from 18 to 64 years and the average was 34 years (Fig. 1). There were 16 men and 21 women. Twenty-two of these patients were producing sputum containing tubercle bacilli at the time of surgery and in 18 of these people there were organisms which were resistant to the effects of either streptomycin (SM) or isonicotinic acid hydrazide (INAH) or both. All patients had contralateral infiltrative disease ranging from a minimal to a moderate extent. Two patients had contralateral cavities. There were five deaths during the operative and immediate postoperative periods, a mortality of 13.5 per cent, no. 1 to 5 (table 2). There was one late death which occurred 8½ months after operation in a patient who suffered from epilepsy and died at home during a convulsive seizure (table 1). Two (5 per cent) bronchopleural fistulae occurred, no. 6 and 7 (table 2), and there were three patients (8 per cent) with recurrent or persistent disease, no. 8 to 10 (table 2).

Twenty-one patients (57 per cent) are at home and working or capable of working. Three are no longer in the sanatorium, but their activities are limited by shortness of breath, easy fatigibility or painful wound. Seven patients are still confined to a hospital. Four of these are in the convalescent period following surgery and are asymptomatic. In summary, 28 of the surviving 31 patients are free of tubercle bacilli in their sputum.

Three patients are still in the hospital and undergoing intensive drug therapy. One, no. 8 (table 2), has maintained a persistently positive sputum since surgery without x-ray evidence of a cavity or bronchoscopic demonstration of tuberculous endobronchitis. The remaining two patients, no. 9 and 10 (table 2), have recurrent disease. Both developed cavities and these occurred at 2½ and 2 years after resection. One has positive sputum and the organisms are resistant

* USPHS cancer trainee.

TABLE 1

Results of pneumonectomy

Number of Patients	Average Age	Contralateral Disease		Sputum		Operative Deaths	Discharged		Hospitalized for Tuberculosis
		With cavity	Without cavity	Negative	Positive/ Resistant*		Well	Symptomatic	
	yr.								
16 Negro men	40	0	16	5	11/8	3	7	2	4
18 Negro women†	28	2	16	7	11/10	2	11	1	3
3 White women	39		3	3			3		
37 (Total)	34	2	35	15	22/18	5	21	3	7‡

* Resistant to SM and/or INAH.

† One patient died 8½ months after surgery in status epilecticus.

‡ Five patients are sputum negative and awaiting discharge.

TABLE 2

Analysis of complications and mortality

Patient no.	Complication	Drug Therapy*	Sputum	Pathology and Bacteriology of Specimen				Culture	Age	Sex	Side
				Fibrocaseous	Bronchiectasis	Cavitation	Endobronchitis				
									yr.		
1†	Pulmonary embolus 6th day	SM, INAH	Negative	+++‡	++	0	0	Negative	35	M	Right
2†	Hemorrhagic shock	INAH, PAS	Positive	++	+++	0	0	Not done	54	M	Left
3†	Tuberculous pneumonia 10th day	SM, INAH, PAS	Positive/ Resistant	++++	++	++	0	Positive	36	M	Left
4†	Acute pulmonary edema 1st day	SM, INAH, PAS, VIO	Positive/ Resistant	++++	+++	++	+++	Positive	21	F	Left
5	Pulmonary insufficiency and renal tubular necrosis	SM, INAH, PAS, VIO, CYCLO, PZA	Positive/ Resistant	++++	0	++	0	Positive	35	F	Left
6	Bronchopleural fistula 31st day	SM, INAH, PAS	Positive/ Resistant	+++	0	+++	++++	Positive	46	M	Right
7	Bronchopleural fistula 5th day	SM, INAH, PAS, VIO, CYCLO, PZA	Positive/ Resistant	+++	0	+++	++	Positive	47	M	Left
8	Persistent positive sputum 1½ yr	SM, INAH, PAS, VIO, CYCLO, PZA	Positive/ Resistant	++++	0	+	+++	Positive	48	M	Left
9	Recurrent positive sputum 2½ yr	SM, INAH, PAS, PZA	Positive/ Resistant	++++	+	+++	0	Positive	37	F	Left
10	New contralateral cavity sputum negative	SM, INAH, PAS, VIO	Positive/ Resistant	++++	0	++++	+	Positive	41	F	Right

* SM = streptomycin; INAH = isonicotinic acid hydrazide; PZA = pyrazinamide; VIO = viomycin; CYCLO = cycloserine; and PAS = para-aminosalicylic acid.

† Died.

‡ + = bisegmental cavitation; ++ = lobar; +++ = bilobar; ++++ = cavitation of 75 per cent or more of the lung.

to most drugs. The other was found to have an asymptomatic cavity, and no organisms were found in the sputum or on examination of gastric washings. This cavity is responding to drug therapy and sanatorium care by decrease in size.

All the surgical specimens were examined pathologically. Two, however, were treated with special technique to preserve them for teaching specimens and no histologic preparations were obtained. Both of these lungs were almost com-

pletely destroyed, only giant communicating cavities remaining. Cavity sizes were estimated on gross inspection. The diagnosis of endobronchial tuberculosis was made only on the basis of histologic preparations. Since complete serial sections were not obtained, it is possible that this represents a low estimate. Fibrocaseous disease and bronchiectasis were evaluated after both gross and microscopic examinations had been performed (table 4).

Bacteriologic studies were done on 28 of the resected specimens. All cavities and grossly visible caseous foci were sampled. Ziehl-Nielsen slide preparations were made and cultures were obtained by the inoculation of scraped material onto Lowenstein's media. Growth of typical *Mycobacterium tuberculosis* (tables 5 and 6) was shown on 18 of the 28 cultures.

Ventilatory function tests were made in 15 instances. These were performed when review of the patient's course suggested some significant

FIG. 1

TABLE 3

Summary of 37 pneumonectomies

Result	No.	Per Cent
Sputum negative		
Asymptomatic	25	67.50
Symptomatic	3	8.25
Dead	6	16.00
Recurrent disease	3	8.25
Totals	37	100.00

TABLE 4

Pathology of resected specimens

Complication	Gross and Microscopic Evaluation				
	++++*	+++	++	+	0
Fibrocaseous	15	16	4	0	0
Bronchiectasis	2	6	8	4	15
Cavitation	5†	10	11	6	5
Endobronchial	1	5	1	1	27

* + = bisegmental cavitation; ++ = lobar; +++ = bilobar; ++++ = cavitation of 75 per cent or more of the lung.

† Both lungs almost completely destroyed.

TABLE 5

Bacteriology of 28 resected specimens

Smear positive, culture positive	16
Smear positive, culture negative	4
Smear negative, culture positive	2
Smear negative, culture negative	6

TABLE 6

Comparison of sputum and specimen cultures

Sputum positive, specimen positive	14
Sputum negative, specimen negative	8
Sputum negative, specimen positive	4
Sputum positive, specimen negative	2

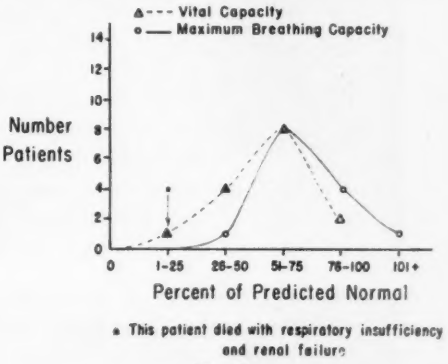

FIG. 2

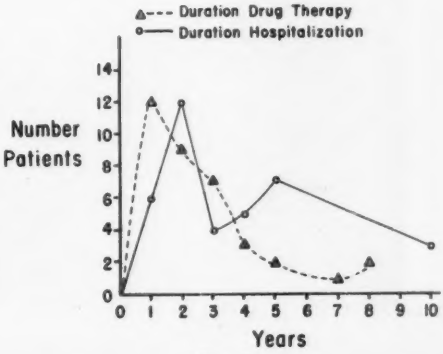

FIG. 3

degree of respiratory insufficiency. The criteria for testing included the presence of elevated hematocrit level, dyspnea on exertion, electrocardiographic evidence of right ventricular hypertrophy or strain and bilateral infiltrations at the time of initial x-ray examination. The results of two of the modalities tested, vital and maximum breathing capacities are plotted in figure 2. Most of the patients suffered a 25 to 50 per cent reduction in these capacities.

The shortest duration of total hospital stay was 8 months and the longest was 11 years. The plot in figure 3 for duration of hospitalization shows two peaks, one at about 2 years and the other at 5 years. It is felt that this is due to the continued presence of some patients who acquired tuberculosis prior to the widespread adoption of surgical therapy. In future series this should not be present and the first peak will probably be displaced farther to the left. The average durations of hospital stay and antibiotic therapy were 3 years and 9 months and 2 years and 6 months respectively. In the more recent cases these durations were identical. The difference in the averages is contributed by those people first hospitalized in the preantibiotic era.

The x-ray findings varied considerably in these cases. A few examples will facilitate an understanding of the problems. Some presented massive destruction of the lung with replacement by giant cavities. This can be appreciated from figure 4*A*. The entire left lung in this 39-year-old male patient was destroyed and replaced by large communicating cavities. Figure 4*B* shows the same patient after pneumonectomy.

Others were thought to have some functional

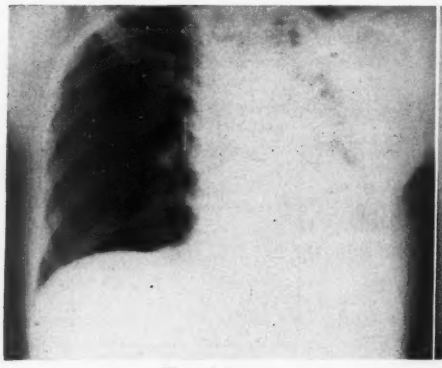

FIG. 4*A*

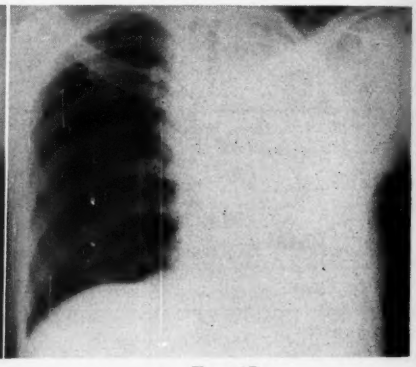

FIG. 4*B*

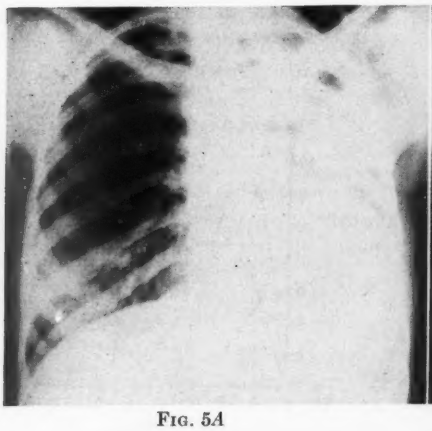

FIG. 5*A*

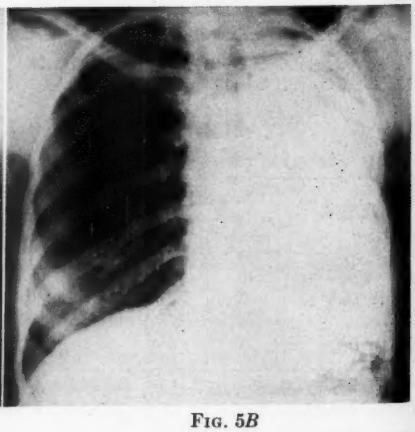

FIG. 5*B*

lung tissue as demonstrated in figure 5*A*. At operation, the left lung of this 26-year-old female was found to have bilobar cavitation. This was restricted to the entire apical-posterior segment of the upper lobe and the superior segment of the lower lobe. The remaining pulmonary parenchyma was firm and incompletely aerated. Diffuse fibrocaseous disease was apparent and a pneumonectomy was performed. The postoperative chest x-ray photograph is seen in figure 5*B*.

Figures 6*A* and 6*B* demonstrate the x-ray findings in a 25-year-old man who was treated with a thoracoplasty elsewhere 6 years prior to resection. Positive sputum recurred one year before pneumonectomy was carried out. This patient, as well as the two preceding, is now completely rehabilitated.

Postoperative tuberculous pneumonia which caused the death of a 36-year-old man is illustrated in figures 7*A* and 7*B*, the pre- and post-

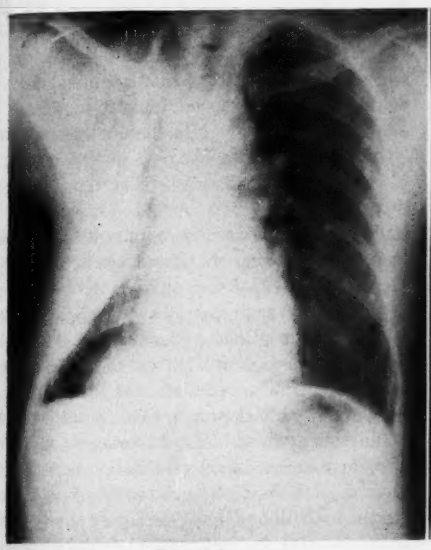

FIG. 6*A*

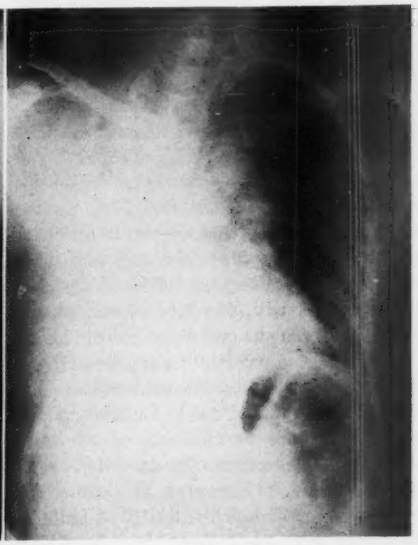

FIG. 6*B*

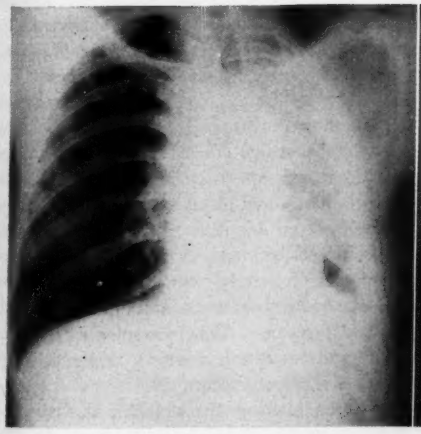

FIG. 7*A*

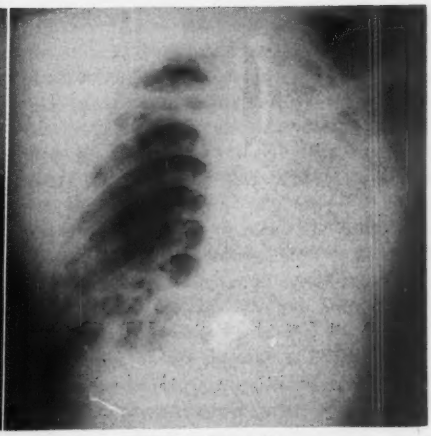

FIG. 7*B*

operative films respectively. The confluent nature of this process resulted in a fatal diminution of functional volume.

DISCUSSION OF MANAGEMENT

1. Drug therapy. The routine use of SM, INAH and para-aminosalicylic acid (PAS) in *all* cases without regard to the *in vitro* sensitivity of the organisms is mentioned only to condemn it. One death and a late bronchopleural fistula, patients 3 and 6 (table 2), in this series might have been averted with more precise drug therapy. The death in question was caused by massive tuberculous consolidation of the remaining lung in the immediate postoperative period. The patient's sputum at the time of surgery was positive and the organisms, while sensitive to INAH, were resistant to SM and PAS. The resection was undertaken while the patient received SM, INAH and PAS. In the light of our experience this represents an error. Another antibiotic to which the organisms were sensitive should have been added for this period.

In the patient with the late bronchopleural fistula, the tuberculous organisms cultured were resistant to SM and partially resistant to INAH. The patient had bronchoscopic evidence of endobronchial disease at and distal to the intermediate bronchus. Histologic examination of the transected mainstem bronchus demonstrated endobronchial tuberculous disease at this site which was not suspected preoperatively. Additional drugs should have been given to this patient prior to surgery and in the postoperative period.

INAH is always continued, regardless of sensitivity studies. There is experimental evidence which suggests that organisms which become resistant to INAH are not so virulent as others.[7] The mechanism of this adaptive process is poorly understood and the attenuation in virulence as tested in guinea pigs occurs simultaneously with a decrease in catalase enzyme activity of these organisms.[10]

It has been our practice to close the chest tightly without drainage following pneumonectomy. Immediately upon resumption of the supine position in bed, the side operated upon is aspirated until normal negative pressure is achieved. Before the needle is removed from the thoracic cavity, penicillin and SM are instilled into it. All subsequent aspirations to maintain a mid-line mediastinum are performed in the same way and these antibiotics are again injected. There have not been any cases of empyema *without* bronchopleural fistula despite the fact that in all of these cases at least part of the resection was done in the extrapleural plane.

The preoperative use of appropriate general antibiotics, postural drainage and bronchodilators is also important in the consideration of this complication. Patients with extensive cavitation and bronchiectasis should have the sputum volume diminished as much as possible. Bronchodilators and especially antibiotics such as penicillin and tetracycline are effective in diminishing the population of potentially dangerous secondary bacilli. The reduction in quantity of purulent secretion is extremely important to minimize the spillage into the contralateral lung during the operation. The risks of a postoperative empyema are also diminished.

2. Ambulation. The second patient listed in table 2 as "hemorrhagic shock" developed tachycardia during the induction of anesthesia. For a short period the pulse rate was 140 per minute. It never dropped below 110 per minute. Difficulty in ventilation was not noted and adequate oxygenation did not seem to be a factor. An extrapleural dissection was necessary and the patient's blood pressure fell to unobtainable levels shortly after this dissection was begun. Despite massive blood transfusion, the patient expired in the operating room. These signs during the induction of anesthesia were subsequently noted in other patients and were sometimes associated with a reduction in systolic blood pressure and a narrow pulse pressure. The incidence of this problem for all our tuberculosis surgery amounted to perhaps 5 to 10 per cent of patients. Operations were postponed because it was found that these patients tolerated blood loss poorly and the blood pressure during the operation was exceedingly labile. The two primary etiologic considerations entertained were (1) that these patients had a low blood volume or (2) that this represented an adaptive phenomenon secondary to prolonged bed rest. A program of graduated preoperative activity was started. The patient is made completely ambulatory over a period of two to three weeks. This is coupled with shoulder girdle and breathing exercises under the supervision of a physical therapist.

Since instituting the regimen described, the incidence of hypotension and tachycardia during

induction has dropped to nearly zero, and unstable blood pressure during the operative procedure is no longer a problem.

3. Studies of pulmonary function. As noted previously, the study of pulmonary function was undertaken only when indicated. We found no correlation between the maximal breathing capacity and either mortality or postoperative dyspnea in this series. The patients with the highest and the lowest values are among the postoperative symptomatic group. There is undoubtedly a minimum level of ventilation which is compatible with survival following pneumonectomy; however, it is probably highly individual and dependent upon such factors as age, cardiac status and weight. This minimum probably resides in the range of 25 to 30 per cent of predicted normal. If a patient's ventilatory studies are markedly abnormal but his ability to walk upstairs is good, the latter is usually a more reliable measure of function. It is also important to measure pulmonary function after a period of physical conditioning as outlined above.

Many of these patients demonstrated the pattern expected in emphysema: *viz.*, difficulty in exhaling as manifest by a prolonged timed vital capacity. The oldest patient in this series was found to have vital and maximum breathing capacities which were normal for his age. He was markedly incapacitated due to repeated attacks of asthma. Measurement of his timed vital capacity showed a marked increase in the time required to expire a volume of air equal to his vital capacity. Following surgery, both the vital and maximum breathing capacities were measured at 65 per cent of normal; however, the timed vital capacity was normal. The patient has not had an asthmatic attack since the operation and considers himself free of pulmonary problems at present. Thus although pulmonary volume was reduced, the relief of asthma appeared to be instrumental in alleviating incapacitating symptoms.

When the evidence obtained by the simple studies outlined above is not sufficient, blood gas studies should be carried out. These should include oxygen saturation studies with the patient at rest, during exercise and when breathing 100 per cent oxygen. If the samples taken during rest and exercise show desaturation and the sample taken while the patient is breathing oxygen does *not*, the risks of resection are very great if any functional pulmonary tissue is sacrificed. If the 100 per cent oxygen sample has the normal 1 to 1.5 per cent of dissolved oxygen, this means that the arterial desaturation at rest and with exercise is probably due to diffuse disease and most likely emphysema. If the arterial saturation taken while breathing 100 per cent oxygen is depressed, this suggests a shunt of blood through unaerated lung and resection of this area of lung may be expected to improve the condition. These cases are uncommon because destruction of the lung by tuberculosis usually destroys the pulmonary vascular bed and there is little flow to the destroyed lung. One patient was encountered with arterial unsaturation in this series and he was improved by resection. At operation it was thought there was considerable blood flow through this diseased lung.

One patient had a vital capacity of 25 per cent of predicted normal. Respiratory insufficiency was a difficult problem in the postoperative period and artificial ventilation and a tracheostomy were required. This patient's course was further complicated by renal tubular necrosis. She expired on the 14th postoperative day because of this last complication. She did not require assistance to ventilation for the last 7 days prior to death. In the light of these experiences an arbitrary lower limit which contraindicates pulmonary resection using any one set of function tests cannot be set. Rather, a total evaluation of the patient, including tests of pulmonary function and blood gases, should serve as the surgeon's guide.

4. Blood Replacement. It is axiomatic that blood replacement during surgery should be accurate regarding both time and quantity. The rapid delivery of an excessive quantity of blood into the circulation of a patient undergoing pneumonectomy is to be feared as strongly as inadequate replacement. When one lung must carry the entire cardiac output, acute adjustments must follow in pulmonary circulation. Pulmonary edema may follow overtransfusion. The fourth patient in table 2 received 11 pints of blood and developed pulmonary edema in the immediate postoperative period while receiving the last transfusion. Blood loss in this case was estimated by the surgeon on the basis of the number of sponges used during the procedure. Because the shortcomings of such an approach were recognized, a more accurate method was

adopted. All sponges are used without moistening in saline solution and are weighed. Aspirated blood is collected in calibrated bottles and blood loss is replaced accordingly. There have been no instances of this nature since this method was put in operation.

5. Thoracoplasty. Procedures to reduce the thoracic volume in association with pulmonary resection have been advocated by many including Björk,[3] Hjort,[5] Bickford[1] and Tørning.[13] The advocates of this course have sought to prove that thoracoplasty is instrumental in (1) reducing the incidence of postoperative bronchopleural fistulae and (2) preventing late reactivation of the tuberculous process. In a recent review[2] of 151 cases of pneumonectomy with thoracoplasty, Björk reported 5 postoperative bronchopleural fistulae. However, 3 additional patients required revision of thoracoplasty for infection with the result that skin was opposed to the mediastinum. It was not stated whether these patients suffered from a bronchial leak. Nevertheless, the numerical sum of these complications (8 cases) accounted for 5 per cent of the total number. This is compared with 5 per cent or 2 fistulae in 37 cases in this series. Fifteen cases of disease reactivation were noted in Björk's series and comprised 9 per cent of the total as compared with the virtually identical figure of 8 per cent in this series.

There are theoretic assumptions which have been responsible for the adoption of space diminishing procedures by some surgical schools. On postoperative x-ray examination of the chest, especially in the lateral position, the remaining lung is enlarged. This can be seen best in the anterior mediastinum. The advocates of thoracoplasty consider this a pathologic process related to emphysema with its attendant ventilatory insufficiency. In some cases they find an increase in residual lung volume and consider this detrimental to pulmonary function. Unfortunately there are few presentations of the complete profile of lung volumes in the postoperative period. Obviously if total lung volume increases, an increment of increase may be expected in all contributing volumes. If the ratio, for example, between vital capacity and residual volume, remains the same, then an increase in the latter associated with a proportional increase in the former cannot be classified as abnormal. An increase in lung volume unassociated with the degenerative processes encountered in true emphysema has not been proved to be deleterious. This is well illustrated by the case of the 64-year-old patient whose ventilatory function increased in efficiency following removal of a destroyed lung. Until definite evidence of functional impairment caused by this so called overexpansion is at hand, the additional operations seem unwarranted.

To have patients with far advanced tuberculosis return to a productive role in society is gratifying. Ideally, the aim of such therapy is eradication of the disease without significant loss of function. This is not possible in extensive infection. The ability of the tubercle bacillus to destroy the lung and the nature of the host response to this necrosis preclude the attainment of this ideal result. The surgeon's responsibility in these instances is to remove those areas of destroyed lung which cannot heal with antibiotics alone. The performance of safe extirpative procedures for pulmonary tuberculosis requires, in addition to skill, a profound attention to all aspects of the patient's welfare. The preoperative preparation of a patient must be influenced by the surgeon long before the patient arrives at the operating room. The best possible drug therapy, ambulation and nutrition must be established for each patient on an individual basis. Cardiopulmonary function must be assessed and this dictates the limits of resection. In the enthusiasm to eradicate disease or convert sputum the surgeon must be wary of becoming the executioner or of converting a comfortable patient with a positive sputum to a respiratory cripple with a negative sputum.

SUMMARY

1. Thirty-seven cases of pneumonectomy for tuberculosis have been presented.

2. The operative mortality was 13.5 per cent.

3. There were two instances of bronchopleural fistula, or 5 per cent of the total.

4. Three patients suffered reactivation or persistence of the disease (8 per cent).

5. The problems of the pre- and postoperative management of these cases have been discussed.

Robert Zeppa
North Carolina Memorial Hospital
Chapel Hill, N. C.

REFERENCES

1. Bickford, B. J., Edwards, F. R., Esplen, J. R., Gifford, J. H., Thomas, O. F., and

WADDINGTON, J. K.: A critical review of the results of lung resection for pulmonary tuberculosis. Thorax, *12:* 152, 1957.
2. BJÖRK, V. O.: Pneumonectomy for pulmonary tuberculosis. J. Thoracic Surg., *32:* 528, 1956.
3. BJÖRK, V. O.: Present indications for space-diminishing procedures after pulmonary resections for tuberculosis. Acta chir. scandinav, *112:* 454, 1957.
4. COOLEY, J. C., MOSER, F. H., AND HEDBERG, G. A.: The results of pulmonary resection in the treatment of tuberculosis: An evaluation of 201 consecutive resections. J. Thoracic Surg., *33:* 383, 1957.
5. HJORT, S.: Space reducing procedures in connection with pulmonary resections. Acta chir. scandinav., *112:* 445, 1957.
6. LINDSKOG, G. E., AND LAW, F. D.: Pulmonary resection for tuberculosis. Yale J. Biol. & Med., *23:* 474, 1951.
7. MIDDLEBROOK, G.: Isoniazid resistance and catalase activity of tubercle bacilli. Am. Rev. Tuberc., *69:* 471, 1954.
8. MURPHY, J. D., AND DAVIS, J. M.: Pulmonary resection for tuberculosis, J. Thoracic Surg., *32:* 772, 1956.
9. OVERHOLT, R. H., LANGER, L., SZYPULSKI, J. T., AND WILSON, N. J.: Pulmonary resection in the treatment of tuberculosis, J. Thoracic Surg., *15:* 384, 1946.
10. SCHWEIGER, O., ROMÁN, E., AND SOÓS, I.: Studies on the catalase enzyme of mycobacteria. Am. Rev. Tuberc., *77:* 146, 1958.
11. SWEET, R. H.: Lobectomy and pneumonectomy in the treatment of pulmonary tuberculosis. J. Thoracic Surg., *15:* 373, 1946.
12. THORNTON, T. F., AND ADAMS, W. E.: Resection of lung tissue for pulmonary tuberculosis. Internat. Abstr. Surg., *75:* 312, 1942.
13. TØRNING, K.: Loss of function after resection and collapse treatment of pulmonary tuberculosis. Acta tuberc. scandinav., *33:* 219, 1957.

ENDOCRINE RELATIONSHIPS BETWEEN CHRONIC CYSTIC MASTITIS AND CANCER OF THE BREAST*

NATHAN A. WOMACK, M.D.

Chapel Hill, North Carolina

Chronic cystic mastitis is frequent and varied in its appearance. These lesions usually are not cancerous in nature and except for occasional episodes of pain and tenderness also produce no symptoms that are of great consequence. Their importance to the surgeon is derived chiefly from the fact that certain of these lesions may on physical examination mimic the findings of cancer, and even if they are benign at the time, the fear exists that they may eventuate into cancer. The patient shares wholeheartedly in this fear. As a result there is a great tendency for early excision with microscopic examination of most of these palpable masses. There is much to be commended in this approach, particularly if there is the slightest doubt in the mind of the surgeon concerning the nature of the lesion. Unfortunately, however, to the patient the breast is an organ that lends itself poorly to the mutilation of several biopsies or to prophylactic excision. As a result surgical discrimination must sooner or later assert itself. We can well afford, therefore, to concern ourselves with the fundamental nature of this group of lesions. In this study we shall consider endocrine effects in particular.

Many epidermal cells in certain fixed positions are conditioned by previous forces to be receptive to the effect of chemical changes produced by hormonal stimuli. This receptiveness will be noted in most epidermal tissue but is especially apparent in the breast, the apocrine sweat glands, the hair follicles, skin of the face and the epithelium of the vagina and the uterine cervix. The reaction to this hormonal stimulus will vary with these different epithelia. In this discussion we shall concern ourselves with the breast, and in the breast this reaction is dramatic, as dramatic as the structural differences noted in the breast during childhood and those found during lactation. Yet even in the breast all cells do not respond identically to these stimuli, for different cells or groups of cells may show eccentric effects from such hormone. The reaction may be slow or it may be rapid. It is constantly undergoing change because the breast epithelium is not a static tissue.

While experimental evidence of hypophyseal mediation has at times been suggested, this hormonal action on epithelium, for the most part, seems to be a local one, apparently directly on the target cells. An experiment by Courrier and Poumeau-Delille[14] using the rabbit uterus as a test area, illustrated this well. Virginal female rabbits were given subcutaneous injections of estradiol for six days. This was discontinued and progesterone given daily for four days. Each uterine horn was ligated doubly, producing a closed cavity, and estradiol was injected into one cavity. When the animals were sacrificed, it was noted that the progestational reaction was present everywhere in the uterus except where the estradiol had been placed and where it had come in direct contact with the uterine cells.

The hormones having the greatest effect on breast structure are the estrogens, progesterone and the lactogenic principle from the hypophysis, prolactin. While the statement sounds paradoxic, in the breast these hormones work both synergistically and antagonistically. Without the previous successive action of estrogen and progesterone on the breast parenchyma, the cells are to a great extent resistant to prolactin. Not only is this noted in the experimental animal, but it can be well demonstrated in man. In spite of this synergistic activity between estrogen and progesterone, either of these substances in large enough doses tends to inhibit the action of the other. Without the previous action of estrogen, progesterone does not form an effective acinar system, and yet it is progesterone that inhibits the action of estrogen on the hyperplasia and growth of the duct system to an excessive degree.

* From the Department of Surgery, University of North Carolina School of Medicine, and the North Carolina Memorial Hospital, Chapel Hill, North Carolina.

Presented in part as the Seelig Lecture, St. Louis, Missouri, November 23, 1955.

It is well to recall that estrone and progesterone bear a considerable chemical resemblance to one another and indeed this estrogen[42] can be converted into progesterone just as progesterone is an intermediate substance in the synthesis of cortisone. The ovary can convert testosterone[1] to estradiol, and we must assume, therefore, the presence of an intermediary metabolism between these hormones without their complete breakdown. This may explain those occasions in which a hormone of the steroid type seems to have a lessened or even an opposite effect from the one anticipated. At the present time the magnitude of this intermediary metabolism has not been assessed.

The breast is acted upon by estrogen, at the beginning of adolescence in the female, for perhaps four to six years before progesterone plays a significant role in the development of the lobule system. This latter role begins with the start of the ovulatory cycle. Following the full development of the breast, there is in all probability a certain amount of cyclic change in the cellular structure of the breast subsequent to monthly alterations in the plasma level of estrogen and progesterone, similar to that type of cyclic change seen in the uterine endometrium. This, however, can only be inferred because direct morphologic evidence obtained by well controlled serial biopsies is difficult to acquire. Suggestive evidence, however, can be found in the experimental animal. In the rhesus monkey,[45] for instance, the acini of the breast dilate and there is an increase in lobular size as well as perilobular vascularity during the premenstrual and menstrual phases. Following menstruation there is a regression of the lobule until the next premenstrual phase comes along. It is noteworthy that such changes are absent in the nonovulatory cycle. Similar changes have been noted in the human at different stages of the menstrual cycle and an effort made to correlate this with urinary excretion of androgens and estrogens. The results are indeed suggestive.[37] Additional evidence that such cyclic changes occur in the human breast is obtained in the considerable increase in breast size and turgor during the premenstrual phase. In many instances this is carried to such a degree that the patient experiences considerable discomfort in the breasts, which again generally ceases fairly abruptly following the end of menstruation. Much of this, however, may be vascular effect.

By and large, estrogen effect is best noted on the duct system while progesterone has its effect chiefly on the acini. In some animals acinar formation is entirely a function of the corpus luteum. This may not be completely so in the human being, estrogen probably playing a part. Certainly, it has been shown that estrogen can form acini in the rhesus monkey, even though this is not completely effective. On the other hand, in a recent study of the mammary development in the guinea pig,[3] an animal in which complete mammary development was previously thought possible from the administration of estrogen alone, further development was always observed when progesterone was administered. As a matter of fact, stimulation of lobule-alveolar growth was noted with progesterone alone in high doses. This phenomenon has been observed in other animals. Here again it is possible that one is dealing with hormonal interconversions. The most complete lobular system in most animals is that formed by the action of progesterone on cells previously exposed to estrogen. That all cells of the breast are not equally affected in man can be seen during pregnancy. It usually is from four to five months after gestation has occurred before complete development of the acinar system is present. Involution may follow a similar pattern. Except for stretching of the supporting fascia with subsequent contour change, however, the usual breast recovers from the stress of lactation without a great deal of structural damage.

Toward the end of menstrual activity in the human, ovulation is subject to failure of complete development and anovulatory cycles ensue. There is considerable individual variation, but in most women adequate corpus luteum formation may cease several years before the cessation of considerable estrogen formation. The absence of this progesterone inhibition thus leads to a constant uninterrupted relative increase in the estrogen level. Although the actual amount present may be the same or even less, at such times abnormalities in breast involution or chronic cystic mastitis may occur. This is in contradistinction to the type of regular and diffuse involutional change seen in the breast following oophorectomy in the late thirties or early forties when both hormonal functions are simultaneously removed.

The numerous breast lesions that have now come to be referred to as chronic cystic mastitis all represent variance of a single group of histo-

logic changes, *e.g.*, duct growth as evidenced by epithelial hyperplasia, duct branching and increase in diameter, acinar atrophy and periductal edema and fibrosis. At times there may be secretion within the duct; at times there is also round cell infiltration. The dominant lesion, however, remains within the duct. Thus it can be seen that chronic cystic mastitis has little to do with inflammation and frequently is not related to cysts. The term chronic cystic mastitis, however, has reached such a fixed state in medical nomenclature that no effort shall be made to disturb it.

The morphologic characteristics of the lesion have been well described many times. There are several excellent recent reports to which one may refer.[16, 21, 37, 46] The finding at a particular time seems to depend upon a combination of variables like tissue competence, age of the patient, relative strength of the stimulating factor and the length of time that this factor has been acting. The lesion will therefore vary even in a single individual, depending upon the exact time it is observed, for this morphologic aberration is a dynamic one and may be found to change from month to month. Here is an excellent example of the need of a temporal reference to understand pathologic change.

The lesion of fibroadenoma perhaps best illustrates the factor of tissue competence. Here certain isolated areas of the breast parenchyma present ductal overgrowth and periductal edema and fibrosis, while the remainder of the breast may be only slightly affected, if at all. Again, age of the patient plays an interesting role in this competence. When fibroadenomas occur in the teens or early twenties, they are usually spheric or slightly lobulated and always encapsulated. The fibroblastic stroma is preponderant and edema is outstanding. When this mass has been allowed to persist for a few years, or when it begins in the middle or late twenties, there is much less stromal edema and the collagen is hard. Encapsulation becomes less apparent. When the lesion appears in the early thirties, encapsulation is usually absent and the periductal fibrosis is diffuse, sometimes involving a quadrant of breast tissue.

Here then one encounters a particular area of breast tissue that reacts violently to growth stimulation, a reaction that becomes modified with advancing years and finally disappears altogether. The classical fibroadenoma that begins after the age of 35 is a curiosity. Indeed, fibroadenomas that are not removed, although at first tending to react overly to cyclic change and to pregnancy, eventually atrophy as does the normal breast tissue, although still remaining discrete and encapsulated. An exception occurs when on those rare occasions adenosarcoma develops. Thus, if fibroadenoma is a neoplasm, it is a completely conditioned one, disappearing with removal of the stimulus. As a result there is no evidence of systemic endocrine imbalance relating to the formation of fibroadenomas unless it is a transient one, and this lesion appears to be entirely a local phenomenon relating to variation in breast tissue reaction. In the limited experience that we have had with the treatment of fibroadenomas by large doses of progesterone, there has been little tendency for retrogression.

This is not true in the other benign lesions of the breast that go under the name of chronic cystic mastitis because women with such lesions often give a history of menstrual abnormality and pregnancy may be less frequent than normal. One of the earliest changes to be noted at such a time is atrophy of the acini that extend out from the terminal ducts and form the breast lobules. This acinar atrophy, just as is true of subsequent changes, does not affect the entire lobule system diffusely and equally. At times it may involve an entire breast and at other times only a small segment of a large ductal system. Often there is periductal round cell infiltration and edema noted. The intensity of this lymphocytic reaction can at times be equated with the rate of acinar atrophy.

With the disappearance of the acini, the duct ends become blunted and at times bulbous, giving the appearance on section of small cysts. At other times there is exaggerated branching producing the appearance of an unencapsulated adenoma. Indeed, this phase is called by some adenomatosis or adenosis. This glandular proliferation may in turn be surrounded by proliferating fibroblasts, producing the ductal distortion of so called sclerosing adenosis that on superficial microscopic examination mimics the appearance of early invasive cancer.

Another striking microscopic feature often noted in the dilated ducts is a change in the epithelial characteristics to that of an apocrine sweat gland. The epithelium piles up in a lacelike

papillary manner and exocrine type of cellular discharge changes to apocrine. At times the whole cell may exfoliate into the lumen, producing a holocrine type of secretion, but this is most often seen in later hypertrophic changes. The significance of the method in which this change in secretory discharge is brought about needs more study. It certainly changes with progression toward malignancy. Under estrogen stimulus the duct cells secrete but this secretion differs both morphologically and chemically from true milk, being usually thick and turbid and varicolored. It probably represents a combination of exocrine, apocrine and holocrine elements.

Toward the end of menstrual life, duct dilation may be huge and at times fairly abrupt in onset. This usually affects a single duct, although surrounding ducts are also subject to a milder dilation. On inspection the eccentric dilation of the duct resembles a cyst. These cysts contain a clear fluid, the epithelium is flat, the wall is thin, and on gross inspection there is a bluish sheen. This is the "blue domed' cyst of Bloodgood.

It can be seen that all of the changes noted in chronic cystic mastitis are variants of the same fundamental process. It can also be stated that these changes all represent the effect of estrogen stimulation on the duct system altered by cell susceptibility, age of the patient and strength and length of time of the stimulation.

Much of the evidence for this statement stems from animal experimentation. While we must always be cautious about translating biologic phenomena observed in the lower animal forms to the human being, it is apparent that in regard to estrogenic action of the ductal system of the breast, such is to a large extent permissible. While it is true the changes will differ in various species of animals, and indeed in animals of the same species, nevertheless, the basic changes are universally consistent.

These changes of chronic cystic mastitis and their relation to estrogens have been well documented in the mouse, rat, guinea pig, rabbit, goat, monkey and in man. Only a few of the many references are mentioned. As early as 1930 Goormaghtigh and Amerlinck,[23] by injecting daily into mice an estrogen containing extract from sows' ovaries, reported that after several months there was dilation of the ducts and acini of the breast. For several weeks following the injection of a pure estrogen into monkeys, the picture of gynecomastia was also noted to develop by Geshickter and his co-workers.[22] In mice Burrows[10] found that the earliest effect of the estrogens on the breasts of male mice was a proliferation of the mammary ducts as is seen in gynecomastia. This was rapidly followed by cystic dilation and finally by proliferation of the epithelium of the ducts. These latter changes were noted equally in male and female. Mosinger and Firmo[36] also noted that when repeated doses of estrogen were given to guinea pigs even for as long as three years, no cancer developed, although typical chronic cystic mastitis was described at times with intracystic papillomata. Again, Geshickter[20] noted that estrone administered to rats over a long period of time produced adenosis with cystic change in the breast. This phase of the subject has been well considered by Burrows and Horning[11] in their recent monograph.

Moore, Wattenberg and Rose[35] did serial biopsies over a period of many months on the breasts of men who were being treated with stilbestrol for cancer of the prostate. All of the changes that we have described as typical of chronic cystic mastitis were observed. We ourselves have seen fairly large cysts develop in such patients, many with papillary hyperplasia of the epithelium, others with apocrinelike glands. In none have we observed a true fibroadenoma. In none have we observed lobule development such as that seen following the use of progesterone or occasionally androgens.

In the absence of estrogenic stimulation, the structural picture of chronic cystic mastitis has never been reported to occur, either in the human being or in the experimental animal. By the use of excessive estrogen stimulation, chronic cystic mastitis has been produced both in man and in the experimental animal. It would seem to be a safe conclusion, therefore, that this lesion owes its genesis at least in part to the effect of the estrogenic hormones.

In the human being, if this lesion is associated with estrogenic oversecretion, one should be able to demonstrate in the urine of these patients evidence of an increase in the output of estrogen or abnormality in the configuration of the monthly excretory curve. This has not been consistently possible. Many of the studies that have been done are referred to in a paper by Nathanson[37] and will not be given in detail here. Suffice it to say, the levels noted have been for the most part

within normal range. Such urinary excretion studies are in keeping with clinical and chemical evidence obtained in other ways. In spite of this, the frequency of functional menstrual aberration in patients with chronic cystic mastitis is well recognized, and while these menstrual patterns do not follow any particularly clear cut type, they are highly suggestive of hormonal imbalance.

Since there is no direct evidence of increase in estrogen secretion to explain these lesions, a search should be directed toward the evidence for a decrease in estrogen inhibition. The most likely substance with which to start our search is progesterone. Is there evidence of the existence of progesterone insufficiency, or what is the evidence of the presence of anovulatory cycles in these women?

Chemical determination of the progesterone level in the human being is as yet not too reliable and evidence must therefore be indirect. If such patients did not ovulate regularly, the chance of pregnancy would be lessened. We have already referred to a tendency toward sterility in patients with chronic cystic mastitis. This is particularly true when the disease has an early onset. In 1945 we studied the fertility record of approximately 900 of the Barnes Hospital patients in whom there was microscopic confirmation of chronic cystic mastitis and compared the rate of pregnancies with that of a similar group of women from this same area. This study was never published, but the results indicated that the chance of pregnancy in a woman with chronic cystic mastitis was about half that of a woman of comparable age taken from the general population around St. Louis.

We have previously referred to endometrial evidence of progesterone insufficiency in another paper.[25] We are now enlarging upon these previous observations made concerning the relationship between the state of the endometrium in women with chronic cystic disease and that of the breast. Such a study has obvious deficiencies, and as yet we have not collected enough cases to be of considerable statistic value. If one examines a large enough area of endometrial epithelium just before menstruation in normal women, at times not all cells will be of a secretory type just as all breast epithelium does not respond identically, and critical interpretation of endometrial biopsies is necessary. Nevertheless, it can safely be said that the "uterine lace" picture of progesteronal action is rarely complete during active cystic disease.

Urine studies directed at the quantity of progesterone excretion (represented as pregnanediol) are tedious and expensive, and there are many technical difficulties. Nevertheless, such a study was recently described by Copeland[26] and is of considerable interest. When analysis of the urine collected from an entire normal menstrual cycle in the human being was made, the average amount of estrogen excreted was about 500 rat units (5000 international units), and that of progesterone as pregnanediol averaged about 49.6 mg., varying from 15 to 70 mg. In women with painful breasts, the estrogen output was about normal, while the pregnanediol was considerably decreased. Such was true in Schimmelbusch's disease and in one patient studied with cystic changes.

Several years ago[25] by comparing the absorption spectrum in the ultraviolet range of extracts of normal breast tissue with extracts from areas of chronic cystic mastitis, we noted a decrease in those substances containing a keto group in the third position, while those containing a hydroxyl group in this position showed little change. We interpreted this as representing a possible deficit in the α,β-unsaturated keto steroids, a group to which progesterone belongs, in relation to the benzenoid compounds in which estrogens are found. Such an inference must be accepted with caution because of the lack of selectivity of the analytic method.

It would follow from such observations as we have indicated that benign structural abnormalities of the breast parenchyma may result from a failure of the normal ovulatory cycle as well as excessive estrogen intake or production, and that it is probable that this insufficient secretion of a peripheral estrogen inhibitor such as progesterone is not an infrequent occurrence. If this is true, and should no permanent enzymatic pattern of an adaptive nature develop in the cells, the reaction that results in this disease should be a reversible one, and the condition should be to a large extent preventable, or reversible with antiestrogen therapy. This disease would be a conditioned one. While good results have been observed by some, with progesterone used as an antiestrogen, such has not been consistently true. The answer can be found in the dosage used.

The optimal ratio that exists between estrogen

and progesterone has been studied extensively by Courrier, who has recently given us a valuable review of the subject.[13] Antagonism between the two substances is a sensitive phenomenon that often can begin and end rapidly. The effect of estrogen can sometimes be neutralized by as little as 75 times its weight of progesterone. At other times, the ratio may be 1:1000. This ratio varies remarkably with the zoologic species, as can be seen, for instance, in the effect on the uterus of the rabbit compared to that of the monkey. There may be a marked variation depending on the receptor organ. Indeed, different regions of the same end organ will react differently, as we have noted in the development of fibroadenoma and in the breast during early pregnancy.

In an elaborate series of experiments on the breast growth of the guinea pig, Benson and associates[3] call attention to the fact that the ratio of estrogen to progesterone *per se* is not the chief factor involved, but that absolute quantities of estrogen and progesterone given exert the dominant role in controlling rate in mammary development. They noted optimum mammary growth response with dose levels of 1000 μg. of progesterone and 10 to 50 μg. of estrone, a ratio of 100:1 to 20:1. Estradiol and stilbestrol have a much greater effect on duct development than does estrone, and the ratios would therefore be greater. In the spayed rat optimal mammary growth was obtained with 3000 to 5000 μg. of progesterone in combination with 1 μg. of estradiol,[26, 43, 44] and in the mouse the level of progesterone and stilbestrol for optimal development was 6000 to 10,000 μg. with 1 μg.[48]

Since there are at least several types of estrogens usually present in the human in variable amounts at different times, an accurate dosage of progesterone to acquire the ratio noted in animals is difficult to obtain. It must be very large. Furthermore, there is a fact of absolute values. In experimental studies on vaginal keratinization and breast development it is apparent that there is a maximum amount of estrogen that can be utilized. This has been discussed by Courrier. All above this is without functional effect. Thus, as the amount of estrogen is increased above a critical level, the amount of progesterone does not have to be increased proportionately. If 1 mg. of progesterone will neutralize the entire functional dosage of estrogen on the vagina of the experimental animal, it is evident that this 1 mg. of progesterone will oppose any amount of estrogen that might be given. Such then is the explanation of the absolute value effect in the experimental animal. Here again projection of animal experimentation to the human being must be done with caution. There is evidence, however, that with certain modifications this principle may hold true.

It has been shown that in the immature male rabbit, estrone alone produces dilated ducts. This can be prevented with progesterone in adequate amount.[33, 36] This is true in the mouse and more recently has been demonstrated in the goat.[2] In an effort to affect cystic disease in the human being, we have used progesterone as the antiestrogenic substance in a number of instances. As is apparent the dosage of progesterone used must necessarily be a crude estimate and will vary with different individuals. Our first experience was with pure progesterone in oil, given intramuscularly in 50-mg. doses beginning about two weeks after the start of the previous menstrual period and given on alternate days until the next period began.

At first we limited ourselves to large cysts that could be easily observed. The cysts were first aspirated and the nature of the fluid was noted. If upon microscopic examination it contained neither blood nor epithelial cells and if following aspiration a mass could no longer be felt, treatment was begun. Occasionally when cysts were only a millimeter or so in diameter, aspiration was not attempted, diagnosis being established by history and palpation. Also, occasional patients whose chief complaint was that of pain and who presented little palpable abnormality were treated. Wherever there was any question as to the nature of the lesion or wherever the patient desired, excision was carried out. In this series there were two such instances, the cyst recurring after therapy had been discontinued. The results with progesterone therapy are shown in table 1, and, as can be seen, are effective.

The use of progesterone in oil, because it necessitated several injections each month and because it was expensive, was not completely satisfactory. Long acting testosterone, while an effective antiestrogen, possessed undesirable side effects. More recently we have been using 17-α-hydroxyprogesterone-17-*n*-caproate (Delalutin).*

* Kindly supplied to us by Dr. E. C. Reifenstein, Jr., E. R. Squibb and Sons.

TABLE 1

*Results of treatment of 15 patients with progesterone in oil**

	Macro-cysts	Micro-cysts	Pain	Nipple Dis-charge
Number of patients...	12	4	2	
Previous excision of benign lesion.....	4			
No recurrence after one cycle of treatment.....	10	4	2	
Subsequent reappearance with subsidence after treatment.....	1			
Excision of lesion after treatment†....	2			

* More than one lesion present in some patients.

† One patient wished area excised after it was no longer palpable.

TABLE 2

*Results of treatment of 41 patients with 17-α-hydroxyprogesterone caproate**

	Macro-cysts	Micro-cysts	Pain	Nipple Dis-charge
Number of patients...	18	18	9	6
Previous excision of benign lesion.....	13	1	0	1
No recurrence after one cycle of treatment.....	15	15	8	3
Subsequent reappearance with subsidence after treatment.....	3	1	1	3
Excision of lesion after treatment.....		2		

Two patients in this group subsequently became pregnant.

* More than one lesion present in some patients.

Recent observations[30] suggest that this ester has but little antiestrogenic action as compared to pure progesterone in the prevention of estrogen induced fibroids in the guinea pig. Progestational function seemed undisturbed. In the human being the separation of these two functions is difficult.

This progesterone ester has been given as a single intramuscular injection of 250 mg. Table 2 gives the results with the compound in 41 patients. After three or four successive monthly injections, treatment is stopped and the patient examined at intervals of three months. If at such times cysts recur, and this has occasionally happened, a new cycle of treatment is begun. All treatment can usually be stopped after menopause.

As will be seen in both of these groups most patients responded favorably to three or less monthly injections. The relief of premenstrual breast pain has been noteworthy as has been the cessation of nipple discharge. These observations along with the fact that the cysts do not refill under therapy suggest an effect on duct secretion. It is also of interest that 17 of these 56 patients had had a previous surgical excision of the cystic disease before beginning hormone therapy. That follicle formation in the ovary is not appreciably disturbed is evidenced by the fact that two of these patients subsequently became pregnant and delivered full term babies. In none of the four patients upon whom subsequent excision of the lesion was performed did we feel an adequate amount of hormone had been used.

For some time now we have not treated the blue dome cyst by excision. This has been true also of other types of chronic cystic mastitis in which cellular overgrowth could be excluded. Besides what seems to be a simple and effective way of treating chronic cystic mastitis, we have been particularly impressed by the change in mental attitude of the patient. Much of the menopausal tension is abolished and almost all of the patients call attention to a feeling of serenity. There have been no other side effects noted. These findings are in keeping with the observations of those who have used testosterone therapy in such patients. When testosterone proprionate has been given several times a week for one to two weeks before an expected menstrual period, the relief of breast pain and premenstrual swelling has been apparent in more than three-fourths of the patients. The expectancy of subjective relief from placebo therapy should not be more than 50 per cent.

All women do not develop chronic cystic mastitis when subjected to excessive estrogens. This is true of the experimental animal as well. Therefore, there must be additional factors in the formation of this lesion other than estrogen.

The observations of Greene[24] shed light here. He noted cystic changes in the breast of a Belgian

hare, and a strain was developed by outcross matings in which this lesion was of common occurrence. Cysts frequently occurred abruptly during estrus when there was sterile mating and these often disappeared during pregnancy. The cycle of engorgement and disappearance might be repeated many times before residuary changes of small nodules eventually appeared. These nodules were at first microcysts; later large cysts developed and subsequently cancer. By frequent biopsy studies, the progress was one of cystic disease, noninvasive neoplasia and invasion with termination in metastases. The duration of a particular phase of the progression was a variable factor and not a constant.

It is interesting that, as in the human, the reproductive history in these animals was affected in that there was decreased fertility (reduced in 90.4 per cent of animals during period of mammary disorder); there were gestational disorders in about half and the litter size was decreased. Direct studies on progesterone formation were not made, but the findings are indeed suggestive, just as they are suggestive of the interplay of hereditary factors because these findings are not common to all rabbits.

In whatever forms they might exist, hereditary or other accessory factors seem to be involved in the appearance of chronic cystic mastitis, for estrogens alone will not produce the condition in many animals. What these other factors are remains speculative. It is possible that they serve as the initiating principle and that estrogens act as the promoting or conditioning factor.

Such a promoting factor by estrogen becomes clearly apparent when it is recalled that the process of chronic cystic mastitis undergoes involution following castration or after the menopause when the circulating titer of estrogens begins to fall. Even in the presence of estrogen this involution can be brought about by androgens in proper dosage or a physiologic antagonist such as progesterone, as we have already noted. Thus, just as chronic cystic mastitis is brought on by the estrogen overbalance, it disappears when this effect is withdrawn or neutralized in those breasts where there is no epithelial overgrowth. It is in itself not a precancerous lesion as it is completely reversible. It is not a state of being or an event, but it is a process completely conditioned. It is thus not surgical.

The relationship between long standing chronic cystic mastitis and the development of cancer of the breast, however, has posed a difficult problem. There is not a phase of chronic cystic mastitis that cannot be seen associated with breast cancer. The relationship between the two lesions has been the subject of a number of studies, and it would seem that a comparison between the histologic picture of the lesion and the life cycle of the individual as related to the appearance of breast cancer would supply the answer. This has not been entirely the case. For the most part such studies have dealt with chronic cystic mastitis patients as a group, or rather with patients with chronic cystic mastitis who had the lesion or much of the breast excised. Patients evidencing epithelial hyperplasia have not been segregated. So often in such reports the entire breast has been removed; follow-up studies have been brief; insufficient numbers for statistic purposes studied; only deaths from cancer and not the frequency of the development of cancer reported, or other critical features ignored, making the conclusions often of questionable validity. One of the statistic studies that has obviated many of these criticisms is that made by Warren[17] a few years ago. The Massachusetts death rate for breast cancer was used, and the frequency of cancer was extrapolated and compared to that in women known to have had "chronic mastitis." In spite of surgical excision of the dominant lesion, he noted cancer of the breast appeared 4.5 times as frequently in women with such lesions, who were followed as long as from 5 to 25 years. Studying the records of 1200 women with operable breast cancer, Foote and Stewart[16] found 2.4 per cent had had previous excision of some form of benign breast lesion. On the other hand, 1200 women with nonmammary cancer had had such breast lesions removed in only 1.08 per cent of the instances.

When chronic cystic mastitis is taken as a whole, the results of statistic follow-up studies are therefore suggestive, if not overwhelmingly convincing, that women with such lesions stand a greater chance to develop breast cancer. Nevertheless, the vast majority of women who show chronic cystic mastitis do not develop cancer. Where epithelial overgrowth has occurred, the frequency would probably be more pronounced. Where it had progressed to the extent of producing a bloody discharge from the nipple and where the whole breast had not been excised, Donnelly[15] in a small series of cases noted the

frequency of cancer reached almost 50 per cent, but even here the development of cancer of the breast is not inevitable, in fact, in the experience of others the frequency is much less than 50 per cent. The significance of the age of the patient in whom bleeding from the nipple occurs is too often not considered in such compilations. The bleeding's occurring some time after menopause is of a more serious import.

In the experiments of Greene, referred to earlier, it was noted that in rabbits cancer could develop through the progressive stages of cystic change, epithelial hyperplasia, preinvasive cancer and finally frank invasive cancer with metastases. This seems to be a true sequence of events in many women who develop breast cancer. Does cancer that develops through the progressive stages of chronic cystic mastitis represent a stage of lower biologic potential or at least of different potential than cancer of the breast that does not do so? There is no evidence that such is true. Indeed, some of the spontaneous cancers in rabbits observed by Greene that developed without previous ductal dilation took much longer to declare themselves. Certainly, those human tumors that are preceded by cystic disease seem to spread as slowly or as rapidly as breast cancer of other types. What then is the relationship between chronic cystic mastitis and carcinoma?

We might find some clarification of our troubles if we approach the problem of cancer of the breast as a process and not an event and as being the result of at least two factors, the initiating action and the promoting factor. That there are at least two such factors involved in carcinogenesis in general has been under consideration for some years. It was perhaps first brought out by Loeb but has since been clearly delineated by experiments of Friedewald and Rous,[18, 19] MacKenzie and Rous,[34] Rous and Beard,[39] and Rous and Kidd,[40, 41] who recognized the presence of a two stage process in the development of skin cancer in rabbits. The initiating agents, be they genetic, viral or other forms, produce a cellular change that remains latent until affected by a second situation that may be more or less specific for the particular tumor but which also conditions a situation generally favorable to cellular proliferation. When tar, for instance, was applied to the skin of a rabbit previously exposed to skin papilloma virus, squamous cancer made its appearance at the site where tar was applied. Under ordinary conditions the papilloma would have preserved its benign characteristics, or when tar was applied to normal skin many months would be required even for the appearance of a papilloma. Again, the promoting factor may be nonspecific as is seen when the site of previous tar papillomas was partially excised for biopsy and squamous cancer noted to develop at the point of excision. This concept has been investigated by many since then. Berenblum[4-7] and Berenblum and Shubik[8, 9] have produced evidence that shows wide agreement. When a weak carcinogen, 1:2-benzanthracene, is applied to the skin of mice, as a rule there are no visible effects, or at the most a few long delayed papillomas occur that disappear or remain benign. If at a later date croton oil is applied to this same area, squamous cancer supersedes. Croton oil has been shown to be noncarcinogenic or at the most extremely weakly carcinogenic to the normal skin of mice. Many other illustrative experiments have been performed to substantiate this concept. Foulds[17] has reviewed this approach well and his paper should be referred to.

The process of initiation, then, is a process and not an event. It may act rapidly, almost instantaneously, or it may be slow in action. Whether or not this effect is on the ability of the cell to respire, as was suggested by Warburg, need not be considered here. Suffice it to say its effect is irreversible. The promoting factor, on the contrary, is much slower and in the beginning is reversible. Nevertheless, the changes it evokes are the changes of progression that are qualitative and not just quantitative. With this progression, reversibility becomes a less and less prominent feature until eventually complete independency is gained and the need for the promoting factor is completely lost.

It was apparent from the experiments of Lathrop and Loeb[29] and Loeb[31, 32] that ovarian secretion might serve as such a promoting factor in cancer of the breast. He showed that in a strain of mice, in which most of the females were destined to develop spontaneous breast cancer, this event could be prevented if castration were performed before the advent of estrus. Lacassagne[27] demonstrated that this ovarian secretion was estrogen, and he produced cancer of the breast in the males of a high cancer strain by the injection of estrogen. Again, this development of spontaneous breast cancer in the female

mouse can be prevented by the injection of a powerful estrogen inhibitor, testosterone, as has been demonstrated by Lacassagne and Raynaud.[28] We ourselves have been carrying along similar experiments, and so far, out of a large group of mice of a high breast cancer strain we have noted not a single instance of breast cancer in the testosterone treated animals, while in similar groups used as controls or injected with estradiol, most of the mice have succumbed to tumor. It would seem, therefore, that estrogen does fulfill all of the requirements for a promoting agent in cancer of the breast.

That estrogen does not act as an initiating factor can be demonstrated by its ineffectiveness in producing cancer in mice in which the genetic and milk principles are absent.

In the human being cancer is often observed to appear long after active menstrual function has ceased. This should not be surprising. It has been recently demonstrated that in many women the ovary continues to function as a source of estrogens at a low but significant level long after the menopause.[38] Furthermore, if the action of the promoting factor is related to the establishment of new metabolic pathways, this action may not show itself immediately. There are also sources of estrogen other than the ovary.

Thus, we have estrogen serving as a promoting factor in breast cancer as well as in chronic cystic mastitis.

Chronic cystic mastitis without epithelial hyperplasia is a different lesion from the one in which the epithelium is showing an exaggerated growth response. They must be separated in statistic considerations. Epithelial overgrowth in chronic cystic mastitis is a result of the effect of a promoting factor in the presence of cancer susceptibility of varying degrees. At first this hyperplasia usually is reversible, as has been noted by the fact that following menopause and ovarian atrophy the hyperplasia may often undergo atrophy. This is not always the case, however. This reversibility may be suddenly or gradually lost as progression occurs. At just what stage androgen therapy would cease to bring about this reversibility when epithelial hyperplasia of the precancerous type has developed, we have no way of knowing. In the beginning, as we have seen, the duct cells need estrogens and are impeded by androgens. Later, as progression occurs, neither do the cells need estrogens nor are they impeded by androgens. This apparent development of adaptive enzymes seems to be the essence of the loss of host resistance to the malignant process. This cellular adaptation may or may not be related to metastasis but seems definitely to be related to the growth of metastases. All cancer cells do not have the same metabolic pathways, and similarly, all breast cancer cells apparently do not have the same metabolic pathways. Cells in one part of a tumor will often differ from those in another part as will cells in one stage of their history differ from those in a later stage.

All breast cancers in the human by no means follow the pathway of development through the hyperplastic changes noted in those preceded by chronic cystic mastitis. Perhaps less than a third of them do. Others seem to develop directly from the nondilated duct but the same type of progression seems to exist. This can be seen by the presence of obvious reversibility of many of the cells even after metastases have occurred, as evidenced by latency with later reactivation. We are all familiar with metastases that exhibited themselves many years after the primary cancer has been removed. Again, the withdrawal of estrogens by castration, or adrenalectomy or even hypophysectomy may show its effect on many but not all cancer cells. Similar effects are noted with androgen administration. Other tumors are completely irreversible when first seen. These are the ones with no longer any dependency, and they are not affected by castration or androgen therapy. These are the ones susceptible to heterotransplantation and are not affected by withdrawal of the promoting factor and they kill their host. Cancer of the breast is thus composed of heterogenous components. This has led to considerable difference in the end results of treatment, where small samples are studied, and as a corollary, considerable difference of opinion regarding the proper treatment.

If there are such things as initiating and promoting factors, we can reason that the initiating factor that sets up the potentiality for chronic cystic mastitis is different from the initiating factor of breast cancer. The promoting factor, estrogen, is the same. In one, estrogen results in a conditioned lesion that disappears with the disappearance of the estrogen effect. In the other, the estrogen effect is that of epithelial overgrowth, the promoting action in the development

of cancer that results in cancer progression. Since the promoting factor, estrogen, for each is the same, some women with chronic cystic mastitis will develop breast cancer and others will not, depending upon whether they also possess the initiating factor predisposing to breast cancer. Others will develop cancer without chronic cystic mastitis and some neither. The presence of chronic cystic mastitis will always be tangible evidence of a preponderance of the estrogenic promoting factor and herein lies its significance.

SUMMARY

1. Chronic cystic mastitis develops when a factor of initial susceptibility is followed by a period of long and constant uninterrupted estrogenic action.

2. Chronic cystic mastitis is a conditioned process when not associated with permanent epithelial change. It is thus reversible and this reversion can be brought about by the withdrawal of estrogen or the administration of an estrogen antagonist. At the present, progesterone in adequate dosage seems to be an effective antagonist.

3. The promoting factor for chronic cystic mastitis, namely estrogen, also serves as a promoting factor in the progression of cancer of the breast.

4. If the initiating factor for cancer of the breast happens also to be present in a patient with chronic cystic mastitis, progression into cancer may occur.

5. When cancer of the breast occurs, the withdrawal of sources of endogenous estrogens or the administration of an antagonist such as androgens will be effective only to the extent to which the cancer cells are reversible.

Chapel Hill
North Carolina

REFERENCES

1. Baggett, B., Engle, L. L., Savard, K., and Dorfman, R. I.: Formation of estradiol-17-β-C^{14} from testosterone-3-C^{14} by surviving human ovarian slices. Fed. Proc., *14:* 175, 1955.
2. Benson, G. K., Cowie, A. T., Cox, C. P., Flux, D. S., and Folley, S. J.: Studies on the hormonal induction of mammary growth and lactation in the goat. J. Endocrinol., *13:* 46, 1955.
3. Benson, G. K., Cowie, A. T., Cox, C. P., and Goldzveig, S. A.: Effects of oestrone and progesterone on mammary development in the guinea pig. J. Endocrinol., *15:* 126, 1957.
4. Berenblum, I.: The mechanism of carcinogenesis: a study of the significance of cocarcinogenic action and related phenomena. Cancer Res., *1:* 807, 1941.
5. Berenblum, I.: Carcinogenesis and tumor pathogenesis. Advance Cancer Res., *2:* 129, 1954.
6. Berenblum, I.: A speculative review: The probable nature of promoting action and its significance in the understanding of the mechanism of carcinogenesis. Cancer Res., *14:* 471, 1954.
7. Berenblum, I.: Irritation and carcinogenesis. Arch. Path., *38:* 233, 1944.
8. Berenblum, I., and Shubik, P.: The role of croton oil applications, associated with a single painting of a carcinogen, in tumor induction of the mouse's skin. Brit. J. Cancer, *1:* 379, 1947.
10. Burrows, H.: Pathological changes induced in mamma by oestrogenic compounds (Hunterian Lecture). Brit. J. Surg., *23:* 191, 1935.
11. Burrows, H., and Horning, E. S.: *Oestrogens and Neoplasia.* Charles C Thomas, Springfield, Ill., 1952.
12. Copeland, M. M.: Discussion. Tr. South. S. A., *73:* 239, 1951.
13. Courrier, R.: Interaction between estrogens and progesterone. Vitamins and hormones, *8:* 179, 1950.
14. Courrier, R., and Poumeau-Delille, G.: Antagonisme hormonal par action directe et localisée sur une partie du récepteur. Compt. rend. Soc. de biol., *137:* 361, 1943.
15. Donnelly, B. A.: Nipple discharge: its clinical and pathologic significance. Ann. Surg., *131:* 342, 1950.
16. Foote, F. W., and Stewart, F. W.: Comparative studies of cancerous versus noncancerous breasts. Ann. Surg., *121:* 197, 1945.
17. Foulds, L.: The experimental study of tumor progression, a review. Cancer Res., *14:* 327 1954.
18. Friedewald, W. F., and Rous, P.: The initiating and promoting elements in tumor production. J. Exper. Med., *80:* 101, 1944.
19. Friedewald, W. F., and Rous, P.: The determining influence of tar, benzpyrene and methylcholanthrene on the character of the benign tumors induced therewith in rabbit skin. J. Exper. Med., *80:* 127, 1944.
20. Geschickter, C. F.: Mammary carcinoma in rat with metastasis induced by estrogen. Science, *89:* 35, 1939.
21. Geschickter, C. F.: *Diseases of the Breast.* J. B. Lippincott Co., Philadelphia, 1945.
22. Geschickter, C. F., Lewis, D., and Hartman, C. G.: Tumors of breast related to oestrin hormone. Am. J. Cancer, *21:* 828, 1934.
23. Goormaghtigh, N., and Amerlinck, A.: Réalisation expérimentale de la maladie de Reclus de la mamelle chez la souris. Bull. Assoc. franc. étude cancer, *19:* 527, 1930.
24. Greene, H. S. N.: Familial mammary tumors in the rabbit. J. Exper. Med., *70:* 147 and 167, 1939.
25. Kier, L. C., Hickey, R. C., Keetel, W. C., and Womack, N. A.: Endocrine relationships in benign lesions of the breast. Tr. South. S. A., *73:* 229, 1951.
26. Kirkham, W. R., and Turner, C. W.: The

induction of mammary growth in rats by estrogen and progesterone. Proc. Soc. Exper. Biol. & Med., *57:* 139, 1954.

27. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle, soumise à des injections de folliculine. Compt. rend. Acad. d. sc., *195:* 630, 1932.
28. Lacassagne, A., and Raynaud, A.: Apparition de carcinome mammaire chez des souris subissant un traitement combiné d'oestrone et d'une dose de testostérone 50 fois plus forte. Compt. rend. Soc. de biol., *132:* 431, 1939.
29. Lathrop, A. E. C., and Loeb, L.: Further investigations on the origin of tumors in mice. III. On the part played by internal secretion in the spontaneous development of tumors. Cancer Res., *1:* 1, 1916.
30. Lipschutz, A., Jadrijevic, D., Mardones, E., Figueroa, S., and Giardi, S.: Comparative antioestrogenic potencies of progesterone and esterified 17-alpha-hydroxyprogesterone in the guinea pig. J. Endocrinol., *15:* 248, 1957.
31. Loeb, L.: Further investigations on the origin of tumors in mice. VI. Internal secretion as a factor in the origin of tumors. J. Med. Res., *40:* 477, 1919.
32. Loeb, L.: The significance of hormones in the origin of cancer. J. Nat. Cancer Inst., *1:* 169, 1940.
33. Lyons, W. R., and McGinty, D. A.: Effects of estrone and progesterone on male rabbit mammary glands. I. Varying doses of progesterone. Proc. Soc. Exper. Biol. & Med., *48:* 83, 1941.
34. MacKenzie, I., and Rous, P.: The experimental disclosure of latent neoplastic changes in tarred skin. J. Exper. Med., *73:* 391, 1941.
35. Moore, G. F., Wattenberg, C. A., and Rose, D. K.: Breast changes due to diethylstilbestrol during treatment of cancer of the prostate gland. J. A. M. A., *127:* 60, 1945.
36. Mosinger, M., and Firmo, J. DeO.: Arquivo Anatom. Patol., *34:* 111 and 149, 1947–1948. Quoted from Burrows, H., and Horning, E.: *Oestrogens and Neoplasia.*
37. Nathanson, I. T.: The relationship of hormones to diseases of the breast. Surgery, *16:* 108, 1944.
38. Paulsen, C. A., Leach, R. B., Sandberg, H., and Maddock, W. O.: Function of the postmenopausal ovary: urinary estrogen excretion and the response of administered FSH. Proc. Endo. Soc., June 1955.
39. Rous, P., and Beard, J. W.: The progression to carcinoma of virus-induced rabbit papillomas (Shope). J. Exper. Med., *62:* 523, 1935.
40. Rous, P., and Kidd, J. G.: A comparison of virus-induced rabbit tumors with the tumors of unknown cause elicited by tarring. J. Exper. Med., *69:* 399, 1939.
41. Rous, P., and Kidd, J. G.: Conditional neoplasms and subthreshold neoplastic states. J. Exper. Med., *73:* 365, 1941.
42. Samuels, L. T., Helmreich, M. L., Lasater, M. B., and Reich, H.: An enzyme in endocrine tissues which oxidizes Δ^5-3 hydroxy steroid to $\alpha\beta$ unsaturated ketones. Science, *113:* 490, 1951.
43. Scharf, G., and Lyons, W. R.: Effects of estrone and progesterone on male rabbit mammary glands. II. Varying doses of estrone. Proc. Soc. Exper. Biol. & Med., *48:* 86, 1941.
44. Smith, T. C.: The effect of estrogen and progesterone on mammary gland growth in the rat. Endocrinology, *57:* 33, 1955.
45. Speert, H.: Hyperplastic mammary nodules in the castrate female rhesus monkey. Bull. Johns Hopkins Hosp., *67:* 414, 1940.
46. Taylor, H. C., Jr.: The endocrine aspects of chronic mastitis. Surg., Gynec. & Obst., *74:* 326, 1942.
47. Warren, S.: The relation of "chronic mastitis" to carcinoma of the breast. Surg., Gynec. & Obst., *71:* 257, 1940.
48. Yomada, J., Nagai, J., and Naito, M.: Endocrinol. Japan, *1:* 63, 1954. Quoted by Benson et al.[3]

PROBLEMS IN THE DIAGNOSIS AND MANAGEMENT OF HIRSCHSPRUNG'S DISEASE*

COLIN G. THOMAS, JR., M.D.

Chapel Hill, North Carolina

Unusual and exotic diseases have always attracted considerable attention in medicine, not only because of their inherent challenge, but also because of the opportunity they provide for study of abnormal physiologic mechanisms. This has been particularly true of Hirschsprung's disease, and during the past decade there has been remarkable progress in its further understanding. This progress has been due principally to studies establishing its pathologic basis, thereby permitting differentiation from megacolon caused by organic obstruction and functional constipation.[39] Exacting radiologic criteria for diagnosis and a rational surgical treatment followed these fundamental observations.[5, 18, 37, 38] As a consequence, there are now accumulating reports of the excellent results to be procured by resection of the aganglionic and nonpropulsive segment of the rectum and sigmoid colon.[3, 11, 19, 23, 30, 32, 33, 39, 40] These results are to be contrasted with the morbidity as well as frequent unimprovement associated with former methods of treatment.

Although Hirschsprung's disease has heretofore been regarded as a medical curiosity, it is now estimated to occur once in 20,000 births[4] and may well be even more common since in the past many cases have gone unrecognized. The disease is a serious one attended by high morbidity and mortality. Particularly is this true in infancy and in that form in which there is extensive involvement of the gastrointestinal tract.[1, 6, 14, 17, 21, 27, 41] The mortality in older groups of children is difficult to appraise because of the limited experience of any one observer, brief periods of observation and the previous lack of pathologic criteria for diagnosis. Since growth and development do not diminish but more likely magnify the radiologic manifestations (fig. 1), the infrequency of Hirschsprung's disease in adult life further attests to its serious nature.

Despite symptoms practically always dating to the neonatal period, the diagnosis is usually not considered at this time, and most patients are managed by enemas, laxatives and bulky diets until early childhood. A history of constipation since birth or early infancy, episodes of obstipation and fecal impaction in conjunction with the physical findings of a protuberant abdomen, palpable fecal masses and a normal rectum and anus indicate the diagnosis. Although undernutrition is a common finding, normal growth and development may follow good dietary and bowel management and do not exclude the disease. A familial history has also been reported.[1, 4] Differentiation from other forms of megacolon can ordinarily be made by history with confirmation by the radiologist's demonstrating a rectum of normal caliber, a dilated sigmoid and descending colon with the absence of effective peristalsis in the distal "normal" rectum. About 15 per cent of these children have associated megaloureters.[38]

In sharp contrast to these patients with the chronic form of the disease, are those individuals with acute and severe manifestations in the neonatal period. In this group even with prompt recognition the mortality rate is exceedingly high, varying between 50 per cent and 80 per cent.[9] Symptoms are essentially those of intestinal obstruction. Variations in the extent of the disorder, however, have been recognized only recently and the attendant manifestations have been confusing. It is the purpose of this paper to discuss and illustrate by case reports three aspects of Hirschsprung's disease that are deserving of further emphasis: (1) the diagnosis and management of the disease in the newborn with acute intestinal obstruction as the primary manifestation, (2) the establishment of the diagnosis in patients with a compatible history but equivocal radiographic findings and (3) the occurrence and management of postoperative large intestinal obstruction.

INTESTINAL OBSTRUCTION IN THE NEWBORN AS A MANIFESTATION OF HIRSCHSPRUNG'S DISEASE

The increased interest in Hirschsprung's disease as well as the more precise methods of diagnosis have resulted in recognition of a greater

* From the Department of Surgery and the North Carolina Memorial Hospital School of Medicine, University of North Carolina, Chapel Hill, North Carolina.

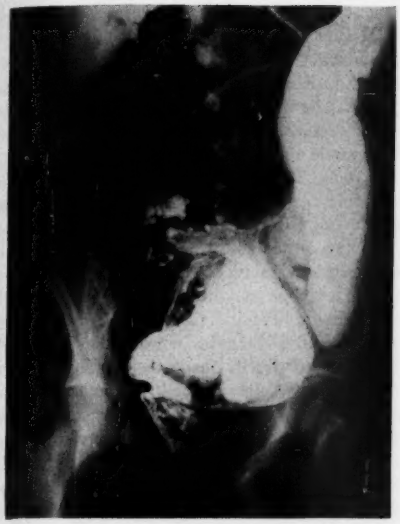

FIG. 1. Classic roentgenographic findings of Hirschsprung's disease as seen in a female of 19 years with a "normal" sized rectum and a dilated and hypertrophied sigmoid colon.

number of patients in the neonatal period. The predominant manifestation has been that of acute intestinal obstruction. This is of such frequency that Hirschsprung's disease must be considered in the differential diagnosis in all cases of large or small bowel obstruction in the newborn. In some series it has been responsible for 25 per cent of cases in this age group—a frequency that parallels that from atresia and malrotation.[40] In attempting to differentiate from other entities such as atresia, stenosis, meconium ileus, volvulus and malrotation, the time of onset of symptoms is of some help since abdominal distention and vomiting in Hirschsprung's disease do not usually appear until the third or fourth day or even later (case 1) in contrast to a more immediate onset in the other situations cited. Physical examination is helpful in that occasionally there is a "palpable narrowing" of the rectal segment,[21] and at times the examining finger may pass into the dilated rectosigmoid segment. Unfortunately the rectum is "snug" in most newborns and particularly so if the distal rectum and rectosigmoid have been "dormant."

Roentgenographic examination of the abdomen may demonstrate the presence of gas throughout the colon but none in the rectum and sigmoid. In those cases in which there is more extensive involvement of the colon, sometimes extending to the cecum (perhaps 10 per cent of all patients with Hirschsprung's disease)[4] the radiologic picture is essentially that of small bowel obstruction.

The pathognomonic radiologic changes with barium enema as seen in early childhood are not present at this time. Dilation and hypertrophy of the colon are functions of time and degree of obstruction. Consequently, these findings are usually not present prior to 4 to 6 weeks and may not be manifest for several months. Even in the newborn, however, there may be fairly characteristic findings.[2, 24] These are a persistent disparity in the caliber of segments of the colon and a conspicuous delay in emptying of the colon so that at 24 hours there is considerable retained radio-opaque material (fig. 4). Furthermore, if the barium reaches and fills the dilated and obstructed bowel regardless of whether it is the distal colon, proximal colon or small bowel, this finding is almost pathognomonic for Hirschsprung's disease. Only to be differentiated would be a "meconium plug" which had been dislodged by the enema.

The newborn with Hirschsprung's disease and manifest intestinal obstruction requires surgical treatment. In the past some patients have been managed by lavage of the dilated segment, employing a soft rubber catheter, or by repeated saline enemas in the hopes of carrying the patient to the age when he is presumably a better operative risk. However, the hazards of repeated bouts of obstruction, which may occur despite detailed care, and the high incidence of superimposed bacterial colitis warrant an immediate colostomy in an effort to reduce the high morbidity and mortality in this age group.

Without surgery the mortality from intestinal obstruction and attendant complications of undernutrition, perforation, peritonitis, volvulus and pulmonary infection is high. The safest and most satisfactory procedure under these conditions is a colostomy at the most distal portion of the normally innervated bowel. A divided colostomy with immediate suturing of the bowel wall to the skin serves to give complete diversion of the fecal stream and a colostomy in which there is immediate function. It is also unattended by the same incidence of prolapse, retraction and bleeding as is occasionally seen with a loop colostomy. Such placement will permit a one stage resection and coloproctostomy at a later date. Satisfactory results have been procured even with

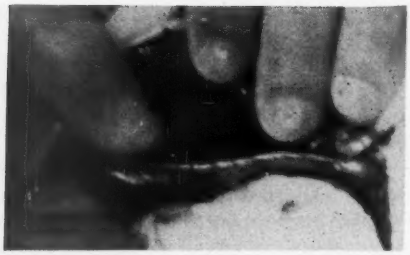

FIG. 2. Operative findings in a patient with meconium ileus depicting the type of conelike narrowing of the bowel commonly associated with Hirschsprung's disease.

involvement of the entire colon and the requisite ileoproctostomy.[34]

Occasionally the diagnosis is not considered until the time of celiotomy for intestinal obstruction. The operative findings may be those of a dilated and gas-filled bowel terminating in a "cone" near the distal rectum or rectosigmoid. In this event a colostomy (or rarely ileostomy) should be carried out through the most distal normally innervated bowel. Confirmation of normal innervation as inferred from the presence of ganglia can usually be made by "frozen section." Ordinarily the operative findings in Hirschsprung's disease are not difficult to differentiate from those in meconium ileus; however, occasionally a coned type of narrowing at the point of obstruction may be present in the latter (fig. 2) and differentiation is facilitated by appropriate biopsy.

Although proctosigmoidectomy has been recommended in the newborn period,[27] the attendant technical difficulties at this time would seem to warrant postponement until greater growth and development have occurred. It is in the newborn in whom the greatest morbidity from the operation occurs as well as the highest mortality with the disease.

The following patients illustrate some of the problems of management in the newborn period.

Case 1. J. E.*, a 5-day-old white male infant, was admitted to the University Hospitals, Iowa City, Iowa, because of increasing abdominal swelling and failure to pass meconium. The most conspicuous finding on physical examination was abdominal distention. Peristaltic sounds were infrequent. Rectal examination allowed the finger to pass into the rectosigmoid without evidence of obstruction. X-rays disclosed barium to outline a normal appearing rectum and slightly dilated sigmoid. The remainder of the colon was filled with gas. Gastric suction was instituted, and efforts made to decompress the colon by means of a long rectal catheter were unsuccessul. Because of failure of improvement, celiotomy was performed the day following admission and extreme distention of the entire colon was disclosed. The entire small bowel was normal. The most striking finding was intense "spasm" of the colon observed at the rectosigmoid junction. The bowel was slowly decompressed with a large bore needle and the abdomen closed. Spontaneous bowel movement occurred 2 days following celiotomy and continued daily thereafter until his discharge on the 14th postoperative day. Roentgenograms approximately 6 weeks later confirmed the diagnosis of Hirschsprung's disease. His subsequent care consisted of enemas given every other day and Urecholine—0.5 mg. 3 times a day. On this regime defecation occurred at 3-day intervals and good results usually followed enemas. At the age of 7 months the patient's weight was 16 pounds and he appeared to be in excellent health. At the age of one year he was readmitted because of findings of a large bowel obstruction. Operation disclosed intestinal obstruction, perforation of the ileum and peritonitis. Recovery followed resection of the terminal ileum. At 2 years of age the descending colon and sigmoid were resected with the anastomosis being done above the peritoneal reflection. Myenteric ganglion cells were present at proximal line of resection but absent at distal line. At age 6 his growth and development were within normal range although he required a daily laxative or cathartic.

Comment. In retrospect the initial barium enema disclosing barium to pass into the dilated sigmoid colon was diagnostic for Hirschsprung's disease, and this patient would probably have been better treated by colostomy at the time of his first operation. His course now suggests an incomplete resection of his aganglionic segment.

Case 2. N. B., a 6-day-old white female infant was admitted to the University Hospitals, Iowa City, Iowa, because of vomiting since birth and the failure to pass meconium. Gestation had been uncomplicated although delivery was thought to be one month early because of premature separation of the placenta. On physical examination abdominal distention was the only abnormal finding. Meconium was noted on rectal examina-

* The surgery on this patient was performed by Dr. R. T. Tidrick.

tion. During the initial week of hospitalization vomiting and abdominal distention continued. X-ray films of the colon, stomach and small bowel were interpreted as normal. Diarrhea developed and became severe. On the 18th hospital day, because of continued vomiting and abdominal distention, celiotomy was performed. Except for a dilated small bowel and a partial constriction near the ileocecal valve no abnormalities were found. A peritoneal fold believed to produce the constriction was divided. Postoperatively the patient had normal stools and retained her feedings for 4 days. Then diarrhea, vomiting and abdominal distention recurred. Six weeks after surgery, a barium enema disclosed small bowel distention with fluid levels (figs. 3 and 4). The patient's subsequent course was unchanged and characterized by severe undernutrition. During the last 6 weeks of hospitalization there was extreme abdominal distention relieved only by the use of Prostigmin. At the age of 8 months the patient became acutely distended and cyanotic and respirations ceased.

At necropsy the small and large intestines were greatly dilated with feces and gas. A segment of sigmoid colon appeared constricted. The rectum and sigmoid colon lacked the normal intrinsic ganglia, whereas the remainder of the gastrointestinal tract was normally innervated.

Comment. Failure to recognize this type of intestinal obstruction as a manifestation of Hirschsprung's disease resulted in inappropriate treatment. A colostomy should have prevented this sequence of events. The development of diarrhea serves to confuse the clinical picture but does not exclude the diagnosis of congenital megacolon. In fact severe diarrhea may be the entering complaint of patients in this age group.[31]

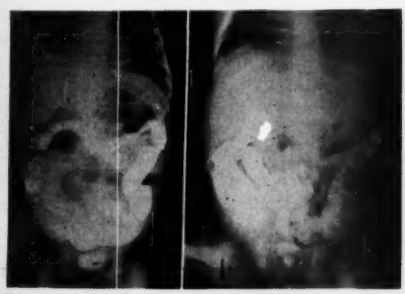

FIG. 3 (*left*). (Case 2) An upright film following barium enema in a 9-week-old female infant disclosed multiple fluid levels in the small bowel as well as a fairly normal appearing colon. The distal rectal segment only is suggestive of Hirschsprung's disease.

FIG. 4 (*right*) (Case 2) The persistence of barium in the colon at 6½ hours (fig. 3) and marked delay in emptying is in keeping with Hirschsprung's disease.

ADJUVANT MEANS OF DIAGNOSIS

The child with a lifetime history of constipation supported by characteristic radiographic findings usually presents no particular problem in diagnosis. Differentiation can usually be made from megacolon due to organic obstruction or chronic constipation. In some groups of patients, however, identification will be difficult and adjunctive measures of evaluation are necessary. Such is encountered: (1) In children in whom a colostomy has already been performed through a normally innervated segment of colon, with the characteristic changes in the distal colon disappearing or failing to develop, and a barium enema disclosing essentially normal findings. (2) In patients with a large dilated rectum, who are ordinarily considered to be examples of functional constipation or organic obstruction at the anal canal. However, some patients with Hirschsprung's disease have been reported in whom the dilated segment of the bowel has extended to the anal sphincter and in whom there has been a favorable response to operation.[19, 28] (3) In the newborn in whom there may be a picture of only partial intestinal obstruction or in whom a coexistent diarrhea may confuse the clinical picture (cases 2 and 5, fig. 8). (4) In a few individuals with coexistent disease such as meconium ileus[10] or pneumotosis cystoides intestinalis[26] in whom a precise diagnosis is necessary for appropriate management.

Adjunctive measures for diagnosis have included balloon-kymographic tracing of intestinal activity, the administration of sympatholytic agents or parasympathomimetic drugs with evaluation of intestinal peristalsis, urinary tract studies and histologic examination of the rectal wall for presence of myenteric ganglia. Our experience with evaluation of peristalsis by balloon-kymographic studies has been limited and unsatisfactory. The multiple balloon techniques facilitated by the presence of a colostomy appear to be diagnostic.[18] A single balloon introduced into the rectum is of little value since the rectal segment is capable of contraction and this ability is apparently enhanced by the use of parasympathomimetic drugs. The use of a sympatholytic agent in an effort to visualize peristalsis in the

sigmoid and rectum has at times been quite valuable. Uniformly, in those instances in which it has been employed in Hirschsprung's disease as observed radiographically, no orderly peristalsis has been visible in the distal or aganglionic segment whereas peristalsis in the dilated and hypertrophied segment has been conspicuously enhanced. With more experience this method may be helpful in differentiation in young infants before the changes of dilation and hypertrophy appear.

By far the most direct aid and the one that provides a precise answer is biopsy of the rectum. This can be carried out directly through rectal mucosa (case 4) or can be performed through an incision immediately adjacent to the internal sphincter without division of the rectal mucosa.[34] This latter method is perhaps better suited to infants and the newborn. Such a biopsy can be done as a separate procedure or can be carried out immediately following ileostomy or colostomy for intestinal obstruction if the patient is in good condition and confirmation of the clinical diagnosis needed. Similarly, in patients with equivocal findings such as those with persistent diarrhea such a procedure will establish the diagnosis. The increased incidence of bacterial colitis in these patients is now being appreciated.[15, 25, 30] There is, therefore, a need for an early diagnosis since immediate colostomy will probably do much toward decreasing the mortality in this age group.

Evaluation of the urinary tract by means of an intravenous pyelogram, cystogram and cystometrogram also should be included since the high incidence of megacystica and megaloureter will serve as corroborative evidence.

POSTOPERATIVE INTESTINAL OBSTRUCTION

In the child the operative morbidity and mortality of proctosigmoidectomy has been quite low. The most troublesome and serious complication has been that of persistent achalasia of the anal sphincter. This may develop in the immediate postoperative period or appear several months to a year or more after an otherwise satisfactory convalescence. The clinical manifestations are those of large bowel obstruction with obstipation, abdominal distention and vomiting. The onset may be acute or insidious covering several days. Episodes of gastroenteritis have preceded the development of this condition in several children. It is particularly hazardous in the small child and has been the chief cause of mortality after completion of convalescence in this age group.[33] Since management is simple and effective by nonsurgical means, recognition of this entity will prevent unnecessary celiotomy, and as in our experience, an unneeded transverse colostomy (case 3).

Case 3. R. M., a 3½-year-old male child was admitted to the University Hospitals, Iowa City, Iowa, because of constipation since infancy. Except for relatively long periods without desire for urination the remainder of the past history was noncontributory. Physical examination disclosed a male within lower limits of normal growth and development. The abdomen was protuberant with a mass extending from the symphysis to the umbilicus. Roentgenograms of the colon indicated Hirschsprung's disease. Following proctosigmoidectomy with the descending colon sutured to the rectum approximately 2.0 cm. from the mucocutaneous line, defecation occurred spontaneously on the 6th postoperative day and continued daily until discharge on the 12th postoperative day. Pathologic examination disclosed absence of ganglia in the distal rectal segment. The patient was readmitted 5 weeks following discharge. He had progressed well until 2 weeks before when bowel movements decreased in frequency. The last normal bowel movement occurred 4 days prior to entrance. There was subsequent decrease in appetite, abdominal distention, vomiting on one occasion, and mild abdominal pain on several occasions. An enema a day during the period of obstipation was without relief. Physical examination disclosed moderate distention of the abdomen, no masses, tenderness or rebound tenderness but it did reveal a visible bowel pattern, hyperactive peristalsis and audible tinkles. Rectal examination revealed an ample anastomotic site admitting two fingers and a dilated bowel proximal to this point. An upright and supine film of the abdomen disclosed dilated loops of bowel with fluid levels (fig. 5). At celiotomy the entire colon was found to be dilated from cecum to the site of previous anastomosis. A decompressive left transverse colostomy was perfomed with the patient's postoperative course being uneventful. Three months later the colostomy was closed and subsequent bowel movements occurred daily. Six months later x-rays disclosed a normal bowel pattern and 12 months later the patient continued to be normal in every respect.

Comment. Since this initial experience we have been more cognizant of postoperative distention

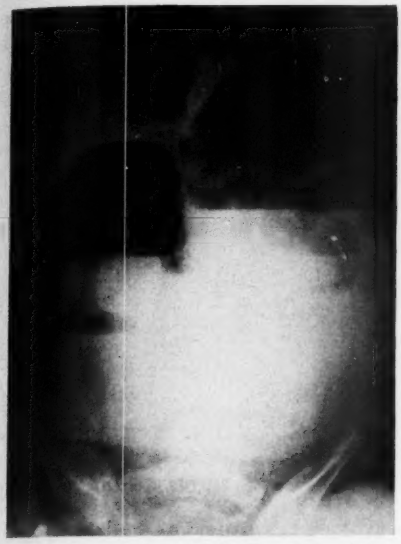

FIG. 5. (Case 3) An upright film of the abdomen 7 weeks after an uneventful convalescence following proctosigmoidectomy discloses evidence of large bowel obstruction which was managed by colostomy. This patient probably could have been treated by mere dilation of the anal sphincter.

simulating large bowel obstruction accompanied by hyperperistalsis, abdominal distention and meteorism. These individuals have not noted severe cramping, abdominal pain, but obstipation has been uniformly present. Roentgenograms may disclose fluid levels. All of these patients have been immediately and dramatically relieved by two finger dilation of the anal sphincter allowing escape of flatus and liquid feces. Subsequent dilation occasionally has been necessary. Small enemas at this time employing a catheter for drainage have apparently been used by Swenson[31, 32] to accomplish the same result. Two examples of this problem with the dramatic response to sphincteric dilation are cases 4 and 5.

Case 4., E. E., a 12-year-old white male patient was seen at the University Hospitals, Iowa City, Iowa, with a history of constipation since infancy, attacks of mild abdominal pain and occasional vomiting, associated with obstipation. His devlopment had been normal and his nutrition was excellent. Roentgenograms disclosed a segment of rectum in which no peristalsis could be visualized. Immediately proximal to this point the sigmoid was dilated four to five times normal size. Pyelograms and cystometrograms were within normal limits. A mass was palpable in the lower abdomen. Rectal examination revealed good sphincter tone and an ampulla that seemed less capacious than normal. Following proctosigmoidectomy and immediate re-establishment of continuity of the colon his course was uneventful for 48 hours. Thereafter, he noted mild cramping, abdominal pain and vomited his evening meal. Peristalsis was hyperactive and tinkles were audible. Nasogastric suction was applied. On the following day there was continued evidence of intestinal obstruction and roentgenograms disclosed marked distention of the left colon (fig. 6). On rectal examination the sphincter was retracted laterally in conjunction with compression of the abdomen and a large quantity of liquid feces and gas escaped. X-rays immediately thereafter revealed complete absence of obstructive findings (fig. 7). The patient's subsequent course was characterized by spontaneous bowel movements which occurred twice daily. There have been no subsequent episodes suggestive of intestinal obstruction or recurrence. On pathologic examination ganglion cells were absent in the distal rectum.

Case 5. E. J., a 6½-week-old colored male infant was admitted to the North Carolina Memorial Hospital with a history of feeding difficulty, questionable obstipation and abdominal distention of three weeks' duration. He had received enemas daily since the 9th day of age. On admission physical examination disclosed a poorly nourished male infant, temperature 98.8°, pulse 130 and respirations 24. The abdomen was distended with hyperactive peristalsis by auscultation. Rectal examination was considered to be normal. X-rays on admission disclosed distended loops of bowel representing primarily the transverse colon. The small bowel was almost com-

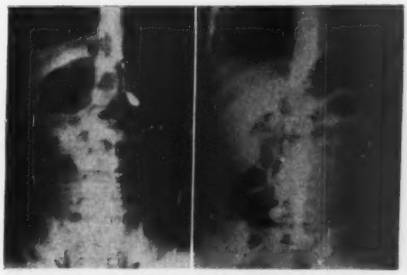

FIG. 6 (*left*). (Case 4) An upright film of the abdomen on the patient's fourth postoperative day disclosed large bowel distention with fluid levels in the small as well as large bowel.

FIG. 7 (*right*). (Case 4) One hour after dilation of the anal sphincter with release of gas and fluid the upright film of the abdomen appeared to be within normal limits (*cf.* fig. 6).

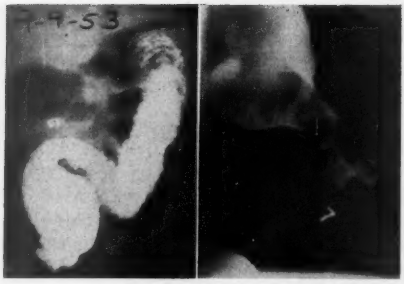

FIG. 8 (*left*). (Case 5) A barium enema in this 7½-week-old male infant with a history of diarrhea since birth disclosed minimal dilation of the colon but a very shaggy appearing mucosal outline.

FIG. 9 (*right*). (Case 5) At 9½ weeks, after control of the diarrhea, a repeat barium enema disclosed the classic findings of Hirschsprung's disease.

pletely outlined with gas; no fluid level was seen except for that in the stomach. No gas was observed in the rectum. A barium enema disclosed a very coarse, fuzzy outline of the mucosa of the rectum and sigmoid. Above this to the level of the cecum, the colon was severely distended (fig. 8).

During the first few days of hospitalization the patient had severe diarrhea with hemolytic *Staphylococcus aureus* being cultured repeatedly from the stools. The diarrhea continued for two weeks with stool cultures becoming negative for Staphylococci after administration of erythromycin. Repeat x-rays showed a narrowed terminal 5 cm. of rectum with proximal dilation of the colon (fig. 9). Discharge occurred after 7 weeks of hospitalization, but readmission was required on two subsequent occasions because of fecal impaction and vomiting. At 9 months of age a proctosigmoidectomy and coloproctostomy were performed.

Pathologic examination disclosed 16.5 cm. of rectum and rectosigmoid with the distal 5 cm. of rectum containing no ganglia although there were plentiful nerve trunks.

The patient's postoperative course was uneventful. At the time of operation the patient weighed 18 pounds. Ten months later he weighed 27 pounds and seemed to be getting along well. During the ensuing 7 months constipation became progressively more severe and was associated with occasional vomiting. After obstipation for 2 days and an acute increase in abdominal distention he was readmitted (fig. 10). Examination at this time disclosed hyperactive peristalsis and a succussion splash. The abdomen was protuberant with visible small bowel "stepladder" pattern. The anal sphincter was tight, no feces were present in the rectum. Anorectal dilation was accomplished on the night of admission with astounding results. Great quantities of gas rushed forth with disappearance of abdominal distention. He was subsequently discharged with no further disturbance. His course has since been excellent.

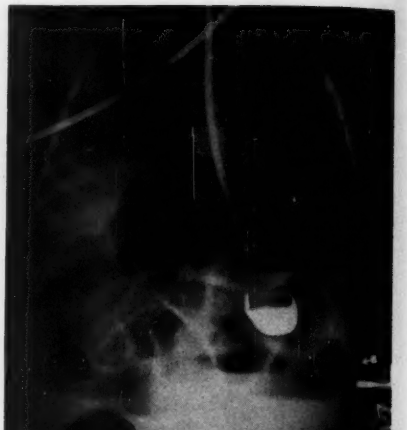

FIG. 10. (Case 5) Seventeen months after proctosigmoidoscopy and coloproctostomy the patient was readmitted with evidence of intestinal obstruction as seen in the flat and upright films of the abdomen. Dramatic relief was obtained by simple sphincteric dilation.

Achalasia of the anal sphincter and large bowel obstruction may develop in the immediate postoperative period or appear several months to a year or more after an otherwise very satisfactory convalescence. The clinical manifestations are those of intestinal obstruction with obstipation, abdominal distention and vomiting. The onset may be acute or more insidious covering several days. Episodes of gastroenteritis have preceded the development of this condition in several children. It is particularly hazardous in the small child and has been the chief cause of mortality after completion of convalescence in this age group. Since management is simple and effective by mere dilation of the anal sphincter recognition of this entity will prevent unnecessary surgical treatment.

DISCUSSION

Since establishment of the pathologic criteria and appropriate surgical treatment of Hirschsprung's disease slightly more than 10 years ago, subsequent progress has been primarily in amplification of the clinical picture and the establish-

ment of more precise indications and contraindications for operation. It is likely that with increasing awareness of the incidence as well as the early manifestations of this disease, few patients will be permitted to progress to the relatively advanced and debilitated state that was synonymous with this problem in years past. However, only an increased suspicion will bring to mind all the vagaries of this disease. Especially is this true in the newborn where enterocolitis seems to be increased in frequency and the attendant diarrhea may mask the expected symptoms of obstipation and intestinal obstruction. A true familial incidence has also been established so that a male sibling has about a 20 per cent chance of having this disease if a proved case already exists in the family.[4]

Additional investigation of the functional changes in the aganglionic segment have revealed disturbances in the normal relaxation-propulsion pattern of the bowel as seen after the administration of a parasympathomimetic drug.[7] Relaxation failed to occur in this segment. Pharmacologic studies have disclosed a much lower amount of substance P (perhaps a local hormone regulating intestinal motility and correlated anatomically with the number of ganglion cells) in the nonpropulsive segment of bowel, whereas increased amounts of substance P have been present in the hypertrophied segments.[13] Other histochemical studies have shown that specific and nonspecific cholinesterase activity is higher in the aganglionic than in the hypertrophied segments. This suggests that the chief anatomic abnormality may be a central displacement of cholinergic neurons with absence or paucity of adrenergic neurons of the myenteric plexus.[20] Since smooth muscle may also be inhibited by high concentrations of acetylcholine,[16] an increase formation of acetylcholine in the aganglionic segment would also account for its change in muscle tone.

Although the pathologic changes in the involved bowel have been clearly established, the etiology of these abnormalities remains obscure. The familial incidence does not differentiate between some genetic abnormality accounting for the neurologic malformation or whether the milieu of development favors such an "injury."

Autonomic ganglia and nerves are related developmentally to the cerebrospinal nervous system, arising from the neural crest. Primordia of the ganglia arise relatively early in embryonic development and those which become sympathetic and parasympathetic ganglion cells are displaced along the efferent roots of nerves that convey the corresponding preganglionic outflow fibers. Consequently, primordia of the prevertebral abdominal plexuses are first seen in the human embryo of 6-mm. length. In the 10-mm. embryo aggregates of cells are conspicuous along the abdominal aorta. However, the primordia of pelvic plexuses are not seen in the human embryo until it is approximately 12 mm. in length.[22] Consequently, any "injury" to the developing nervous system in the 10- to 12-mm. embryo could account for the ganglion deficits seen in the distal rectum and bladder. The fact that although there are variations in the extent of this disease, the distal rectum is consistently involved again, suggests "insult" during this later phase of central nervous system development.

Recently what appears to be a comparable disease of congenital megacolon has been described in mice, with similar pathologic findings and an incidence of 2 to 3 per 1000.[8] The familial incidence was not striking in these animals and the sex distribution was equal.

SUMMARY

Recent developments in the study of Hirschsprung's disease have disclosed a much higher incidence than previously was recognized. Intestinal obstruction in the neonatal period is commonly on this basis and is associated with an extremely high mortality. Complications such as enterocolitis and diarrhea as well as intermittent intestinal obstruction and the high mortality with medical management attest to the need for early surgery. Biopsy of the rectal musculature is a most valuable adjunct to clinical and radiologic diagnosis. Postoperative intestinal obstruction as seen in early convalescence as well as after several years is frequently on the basis of achalasia of the anal sphincter and can be handled by simple dilation. Recognition of the manifestations in early infancy as well as the need for early surgical treatment should not only lower the morbidity and mortality in this age group but also should obviate the progression to more chronic and debilitating stages of this disease.

REFERENCES

1. Berglund, E., Thompson, W. H., and Chisholm, T. C.: Familial absence of the mesenteric plexus as a cause of bowel obstruction in the newborn. Minnesota Med., *39:* 447, 1956.

2. Berman, C. Z.: Roentgenographic manifestations of congenital megacolon (Hirschsprung's disease) in early infancy. Pediatrics, *18:* 227, 1956.
3. Bill, A. H., Jr., Creighton, S. A., and Stevenson, J. K.: Selection of infants and children for the surgical treatment of Hirschsprung's disease. Surg., Gynec. & Obst., *104:* 151, 1957.
4. Bodian, M., Carter, C. O., and Ward, B. C. H.: Hirschsprung's disease, with radiological observations. Lancet, *1:* 302, 1951.
5. Bodian, M., Stephens, F. D., and Ward, B. C. H.: Hirschsprung's disease and idiopathic megacolon. Lancet, *1:* 6, 1949.
6. Bowden, D. H., Goodfellow, A. M., and Munn, J. D.: Hirschsprung's disease in the neonatal period. J. Pediat., *50:* 321, 1957.
7. Davidson, M., Sleisenger, M. H., Steinberg, H., and Almy, T. P.: Studies of distal colonic motility in children. III. The pathology physiology of congenital megacolon (Hirschsprung's disease). Gastroenterology, *29:* 803, 1955.
8. Derrick, E. H., and St. George-Grambauer, B. M.: Megacolon in mice. J. Path. & Bact., *73:* 569, 1957.
9. Dorman, G. W.: Hirschsprung's disease: A lethal problem in early infancy. A. M. A. Arch. Surg., *75:* 906, 1957.
10. Ehrenpreis, T.: Meconium ileus and Hirschsprung's disease. Acta paediat., *40:* 227, 1951.
11. Ehrenpreis, T.: Rectosigmoidectomy for Hirschsprung's disease. Acta chir. scandinav., *102:* 251, 1951.
12. Ehrenpreis, T.: Hirschsprung's disease in the neonatal period. Arch. Dis. Childhood, *30:* 8, 1955.
13. Ehrenpreis, T., and Pernow, B.: On occurrence of substance P in the rectosigmoid in Hirschsprung's disease. Acta physiol. scandinav., *27:* 380, 1952.
14. Forshall, I., Rickham, P. P., and Mossman, D. B.: Functional obstruction in the newborn. Arch. Dis. Childhood, *26:* 294, 1951.
15. Goldbloom, A., and Wiglesworth, F. W.: Hirschsprung's disease (congenital aganglionic megacolon)—Report of three cases in infancy associated with acute colitis. Acta Paediat., *43:* 324 (Supp. 100), 1954.
16. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics.* The Macmillan Company, New York, 1941.
17. Hays, D. M., and Norris, W. J.: Congenital aganglionic megacolon. California Med., *84:* 403, 1956.
18. Hiatt, R. B.: The pathologic physiology of congenital megacolon. Ann. Surg., *133:* 313, 1951.
19. Hiatt, R. B.: The surgical treatment of congenital megacolon. Ann. Surg., *133:* 321, 1951.
20. Kamijo, K., Hiatt, R. B., and Koelle, G. B.: Congenital megacolon—A comparison of the spastic and hypertrophied segments with respect to cholinesterase activities and sensitivities to acetylcholine, DSP and the barium ion. Gastroenterology, *24:* 173, 1953.
21. Klein, R. R., and Scarborough, R. A.: Hirschsprung's disease in the newborn. Am. J. Surg., *88:* 6, 1954.
22. Kuntz, A.: Origin and early development of the pelvic neural plexuses. J. Comp. Neurol., *96:* 345, 1952.
23. Lee, C. M., Jr.: Megacolon—Present concepts. S. Clin. North America, *35:* 1245, 1955.
24. McDonald, R. G., and Evans, W. A., Jr.: Hirschsprung's disease—Roentgen diagnosis in infants, A. M. A. Am. J. Dis. Child., *87:* 575, 1954.
25. Moriarty, L. R., and Ramsey, B. W.: Membranous colitis in two cases of Hirschsprung's disease treated with large doses of antibiotics. Pediatrics, *15:* 438, 1955.
26. Paris, L.: Pneumatosis cystoides intestinalis in infancy. J. Pediat., *46:* 1, 1955.
27. Potts, W. J., Boggs, J. D., and White, H.: Intestinal obstruction in the newborn infant due to agenesis of the myenteric plexus. Pediatrics, *10:* 253, 1952.
28. Ragins, H., and Van Prohaska, J.: Megarectum. Ann. Surg., *145:* 249, 1957.
29. Smith, C. C. W.: 7 Tilfaelde of abdominalanal sigmoideum rectum resection of Hirschsprung's megacolon. Ugesk. laeger., *112:* 216, 1950.
30. Stephens, F. D.: The diagnosis and management of Hirschsprung's disease. Ann. Roy. Coll. Surgeons England, *7:* 257, 1950.
31. Stockdale, E. M., and Miller, C. A.: Persistent diarrhea and predominant symptom of Hirschsprung's disease (congenital dilatation of colon): Report of 2 cases. Pediatrics, *19:* 91, 1957.
32. Swenson, O.: Congenital megacolon (Hirschsprung's disease); follow up on 82 patients treated surgically. Pediatrics, *8:* 542, 1951.
33. Swenson, O.: Congenital megacolon. Advances in Pediatrics, *7:* 325, 1955.
34. Swenson, O., and Fisher, J. H.: Treatment of Hirschsprung's disease with entire colon involved in aganglionic defect. A. M. A. Arch. Surg., *70:* 535, 1955.
35. Swenson, O., Fisher, J. H., and MacMahon, H. E.: Rectal biopsy as an aid to diagnosis of Hirschsprung's disease. New England J. Med., *253:* 632, 1955.
36. Swenson, O., MacMahon, H. E., Jacques, W. E., and Campbell, J. S.: A new concept of the etiology of megaloureters. New England J. Med., *246:* 41, 1952.
37. Swenson, O., Neuhauser, E. B. D., and Pickett, L. K.: New concepts of the etiology, diagnosis and treatment of congenital megacolon (Hirschsprung's disease). Pediatrics, *4:* 201, 1949.
38. Swenson, O., Rheinlander, H. F., and Diamond, I.: Hirschsprung's disease: A new concept of the etiology. New England J. Med., *241:* 551, 1949.
39. Whitehouse, F. R., and Kernohan, J. W.: Myenteric plexus in congenital megacolon: Study of 11 cases. A. M. A. Arch. Int. Med., *82:* 75, 1948.
40. Wyllie, G. G.: Course and management of Hirschsprung's disease. Lancet, *1:* 847, 1957.
41. Zuelzer, W. W., and Wilson, J. L.: Functional intestinal obstruction on a congenital neurogenic basis in infancy. Am. J. Dis. Child., *75:* 40, 1948.

MANAGEMENT OF FACIAL FRACTURES IN UNCONSCIOUS PATIENTS*

ERLE E. PEACOCK, JR., M.D.

Chapel Hill, North Carolina

The management of facial fractures in patients with a serious brain injury is frequently complicated by prolonged unconsciousness and bizarre behavior. The care of such patients is exacting and many reliable methods of reduction and fixation may be ineffective or dangerous during coma or excited states. Some fractures require early reduction before fibrous fixation creates irreparable cosmetic and functional deformity; yet general anesthesia and major manipulation may be fatal during critical stages of an unknown brain injury. Sound judgment based on broad experience is necessary to time and select operative procedures. In the absence of extensive soft tissue wounds, combined face and brain injuries usually are managed entirely by a neurosurgeon at first. As soon as recovery appears certain, however, facial deformity assumes tremendous importance, frequently too late to adjust delicate bones outlining distinctive features. Combined plastic and neurosurgical management from the outset is ideal, particularly if both specialists are trained in the reactions to injury of the facial structures and the central nervous system.

PREOPERATIVE EVALUATION AND CARE

Provision of an adequate airway assumes precedence from the beginning. A common error is to place patients in a supine position where blood, saliva, loose teeth or bone fragments may dislodge and fall unobserved into the upper air passages. Since deeply comatose patients may expire with no warning during mild transient hypoxia, transportation must be in a prone position with constant observation. Tracheotomy may be avoided in the absence of extensive damage to the upper air passages, but rapidly developing edema around the oral and nasal cavities demands early tracheotomy in most patients. Tracheotomy should not be procrastinated in questionable cases, because too often airway encroachment may be superimposed on a condition where anoxia is lethal. This demands maximum preventive measures.

During or following neurologic evaluation the face and nasopharyngeal cavities can be examined without interfering with general supportive treatment or neurologic tests. Facial x-rays are not essential, but when a patient has to be moved for skull films, it is worthwhile to expose a Water's view of the face at the same time that a PA view of the skull is obtained. Good mandible films are difficult to secure under ideal conditions, and the information gained under any other circumstances is seldom worth the added delay and manipulation. Careful inspection and palpation of the alveolar ridges followed by a test of occlusion reveals the majority of jaw fractures.

To detect a fracture of the upper jaw a firm but controlled force should be applied to the upper arch which may be circumferentially intact yet move vertically or horizontally indicating a separation of the middle third of the face. Standing at the head of the stretcher and palpating with both thumbs it is helpful to compare the height of the malar eminences. The complete orbital rim should be palpated to detect fracture crevices before edema develops. Abnormal temporomandibular joint motion and crepitation are occasionally detected by placing the tip of the little finger in the external auditory meatus while the joint is being passively exercised. Depressed fractures of the zygomatic arch may limit excursion of the mandibular condyle, being accurately diagnosed by this test alone. Nasal bone fractures and cartilage distortions are diagnosed by gross deformity, mucosal tears and crepitation. Rhinorrhea should be specifically searched for as it is often overlooked in unconscious patients in the prone position.

After complete evaluation, the face should be gently cleansed and soft tissue wounds dressed. Cold compresses applied to the orbital region will aid in preventing further edema and should not be omitted in unconscious patients. Prevention of orbital edema is especially important after brain injury because significant eye signs

* From the Department of Surgery, University of North Carolina School of Medicine, the North Carolina Memorial Hospital, Chapel Hill, North Carolina.

may be depressed or lost as periorbital tissues become distended. The author has not been impressed with the use of drugs in reducing edema, but favorable results have been reported following administration of promethazine hydrochloride* and hyaluronidase.† [1, 2, 5] The oral cavity should be cleansed with some mild antiseptic solution every few hours. A combination of suction and small amounts of introduced solution will cleanse the area without danger of aspiration. The lips should be protected against drying by a thin layer of cold cream or mineral oil. Large gaping mucosal tears and bone defects in the upper sinuses should be irrigated gently to dislodge dirt or bone fragments that might relocate in the lower airway. Bleeding is seldom a serious problem, although hemorrhage from the internal maxillary artery occasionally requires a temporary gauze pack. Badly displaced or unsupported mandibular fragments should be stabilized temporarily with a Barton type of external gauze dressing. Large doses of aqueous penicillin (in the range of one million units) administered every three hours are more effective in preventing secondary infection than smaller doses of long acting preparations. A broad spectrum antibiotic provides additional coverage and, of course, appropriate tetanus immunization is mandatory in unsensitized individuals.

The preoperative management of facial injuries is essentially an effort to prevent complications by maintaining strict cleanliness. Following tracheotomy a common error is neglect of the oral cavity, allowing blood, saliva and devitalized tissue to form a veritable cesspool of bacterial activity. The organisms which grow in this environment are difficult to erradicate once infection supervenes, and, therefore, continuous or frequent mechanical cleansing is an important preventive measure.

TIMING

Avulsion of the eyelids exposing the cornea is the only facial injury requiring emergency restoration. As little as 30 minutes of exposure following such an injury may result in corneal ulceration and subsequent opacity. Patients with eyelid avulsions and a brain injury which requires immediate surgery should be accompanied to the operating room by an attendant moistening the cornea with a continuous saline drip. As soon as cranial decompression has been completed, the cornea should be protected by suturing lid fragments together or shifting a local skin flap across the eye. Adequate coverage without tension must be obtained, and such procedures can be performed on the ward if the patient's condition does not permit transportation to the operating room.

Small, soft tissue wounds should be sutured as early as possible. Complicated restorations which probably will require secondary adjustment regardless of when they are repaired should be delayed until the patient shows considerable recovery from the brain injury. Blood supply to the face is so good that properly dressed wounds protected by suitable antibiotics can be repaired many days following injury with little significant compromise in the end result.

Fractures requiring early reduction are those of the orbital rim, inner canthus and nasal bones. Membranous bone heals by fibrous union so that it may be impossible to reduce fractures of these bones after six or seven days. Of special importance is the delicate insertion of the medial canthal ligament, for failure to replace the medial wall of the orbit and insertion of the canthal ligament obliterates depth on the sides of the nose. Failure to restore this feature as an initial procedure results in a characteristic broadness between the eyes that is not amenable to secondary correction. Comminuted fractures in the floor of the orbit and dislocations of the zygoma become fixed in approximately seven days, but are not so disastrous in that secondary restorations are generally successful. An additional reason for elevating depressed fractures of the zygomatic arch is to release the temporomandibular joint. Firm ankylosis may develop secondary to fibrous reaction around spicules of bone driven into the pericapsular structures. Upper jaw fractures should be reduced in about 10 days if permanent elongation of the face is to be avoided. Fractures of the mandible have been satisfactorily reduced after four weeks with no ill effects. Exposed bone is a potential site for osteomyelitis, however, and where bone is protruding into the oral cavity reduction and

* Phenergan hydrochloride, promethazine hydrochloride, is available from Wyeth, Inc., Philadelphia, Pa.

† Hyaluronidase is available as Wydase (lyophilized and stabilized solution) from Wyeth, Inc., Philadelphia, Pa.

coverage is more of an immediate problem than for simple fractures.

Facial fractures, excepting nasal bones, are usually best reduced under a general anesthetic, particularly in hyperactive, uncooperative individuals. Selection of the safest time to administer general anesthesia is possible only after the general neurologic course has been determined. Even comatose patients who are clearly improving can be anesthetized safely as long as hypoxia is avoided. Coma, *per se*, is not a contraindication to general anesthesia, but a waxing and waning of the general condition may be a serious sign and during this period general anesthesia is dangerous. Hyperactivity is the main indication for general anesthesia and patients who are in deep coma at the end of five or six days may have some fractures reduced and fixed with no anesthesia. Fortunately, most brain injuries will have passed through a critical stage and will be recovering by the seventh day so that general anesthesia affords no untoward risks.

The correct timing for facial manipulations may be summarized as follows: Small, soft tissue wounds should be closed immediately for best results. Extensive soft tissue restorations can be safely postponed for many days with no significant ill effects. Most head injuries that recover will show definite improvement during the first week and reduction of facial fractures should be delayed during this period. Fractures of the fine bones of the face, particularly the orbit and cristae lacrimalis, must be reduced within the first week, with or without general anesthesia, depending upon the neurologic status. Maxillary fractures also have to be reduced in seven to nine days and since this necessitates interdental appliances, tracheotomy is essential for comatose patients. Mandibular fractures can be delayed four weeks if necessary providing adequate precautions are taken against osteomyelitis.

OPERATIVE METHODS

Facial fractures in unconscious patients should be stabilized without resorting to interdental fixation or external apparatus. Oral hygiene, artificial feedings and the danger of aspiration militate against the usual practice of wiring teeth in occlusion. Projecting hooks, splints and headcaps can be quickly dismantled by excited or disoriented patients and even become instruments of self-destruction. It is recommended that facial fractures in such patients be approached directly and stabilized by simple internal methods. An exception is the badly displaced or comminuted fracture of the upper jaw which requires the lower arch for accurate reduction and temporary fixation. Upper and lower banded arch bars with simple rubber band connection afford greater safety than interdental wires as rubber bands can be removed quickly by inexperienced attendants. Where it is absolutely essential to wire the teeth in occlusion, tracheotomy is mandatory.

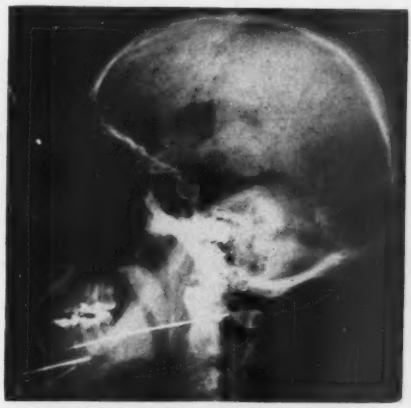

FIG. 1. Symphysis and angle fractures of mandible treated by internal Kirschner wires. Note multidirectional wires at symphysis. Posterior wire is too high and was removed after x-ray.

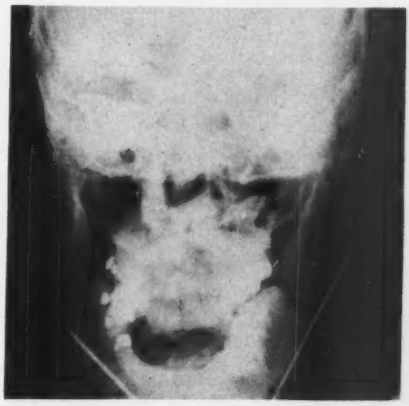

FIG. 2. Single wires holding bilateral angle fractures. The left wire has engaged only the periosteum which is frequently adequate for this fracture.

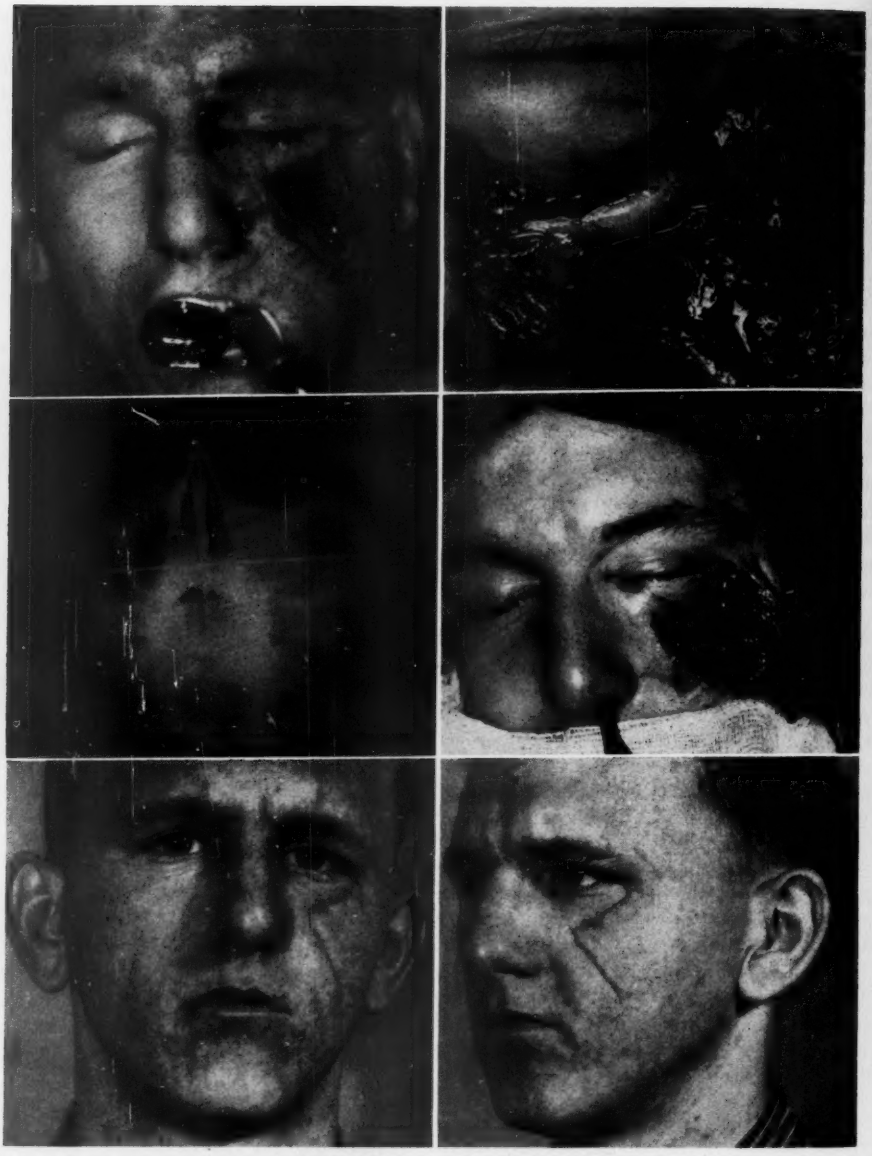

FIG. 3. *Top left*, compound comminuted fractures of the orbital rim, zygomatic arch and maxilla. The entire left side of the face is unstable. *Top right*, operative view of inferior orbital rim showing three bone fragments wired into correct position with no. 26 steel wire. Lateral and superior fragments were wired similarly through separate incisions. Note the antral pack which will support smaller bone fragments placed around it. *Center left*, x-ray of same patient shown in *top left* and *top right*. The orbital rim has been restored and fixed with multiple no. 26 steel wires. The transverse Kirschner wire maintains horizontal position of the orbit and also stabilizes the antral pack. *Center right*, final operative view at time of soft tissue closure. Note antral pack extending out of left nostril, transverse wire protruding from left malar eminence, and supraorbital incisions used to restore upper orbital rim. *Bottom left*, postoperative view of patient six weeks after accident. The soft tissue scar will probably require a future revision. *Bottom right*, left oblique view of patient shown to the left.

Mandibular fractures are usually best fixed by internal Kirschner wires as described by Brown and associates.[3] The wires should be drilled with a high speed electric drill and a minimum of two wires should be used in the region of the symphysis. Wires should not cross at fracture lines, as rotation will still be possible (fig. 1). The ends of Kirschner wires should be clipped flush with the skin. In very unstable fractures in patients with severe central nervous system damage, a single temporary wire can be drilled across the fracture site without taking the patient to the operating room. Posterior fractures between the molars and the angle with the ramus are best drilled from posterior to anterior direction. Inserting a posterior wire is technically a difficult feat, but when successful affords excellent immobilization with a single wire. Occasionally the wire will miss one fragment but will engage the periosteum so tightly that fixation is adequate (fig. 2). The only other alternative under these circumstances is to expose the fracture site and

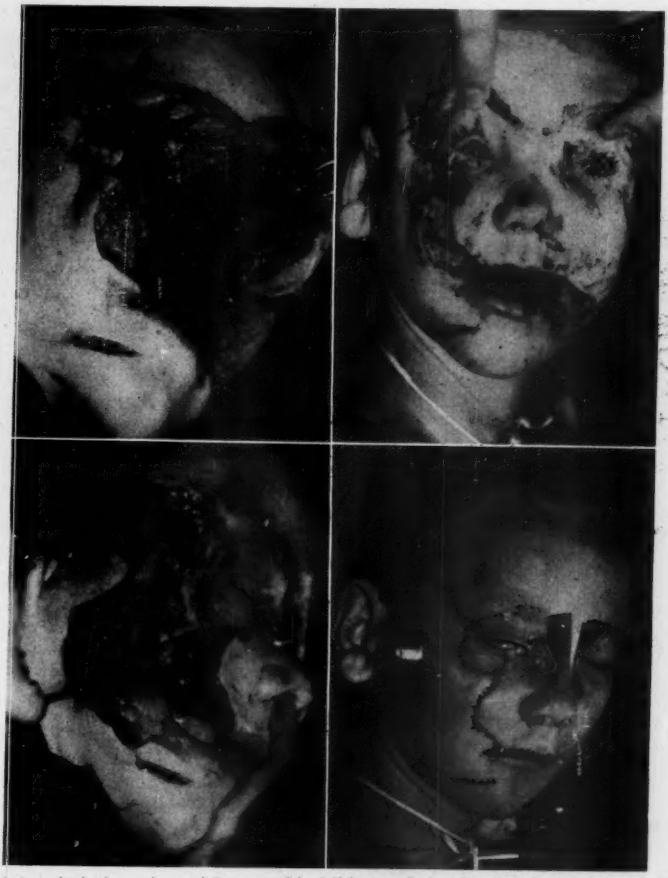

FIG. 4. *Top left*, admission view of 7-year-old child struck in the face by an automobile. The chin is in the lower center of the photograph. The upper jaw, palate and right orbit and zygomatic arch are missing. *Top right*, admission view of face shown to the left after the soft tissue had been pulled back into proper position. The left nasal bone and orbit remain intact, but both maxillae, the right nasal bone and the right orbit were destroyed. *Bottom left*, operative view three days later. A large fragment of the right malar bone was found in the nasopharynx and has been fixed in fair position with two Kirschner wires. A nasal pack supports the soft tissue over the middle third of the face. *Bottom right*, final operative view showing soft tissue closure and lead plates over adhesive tape padding to support the inner canthal ligament attachments. A plastic conformer is in the right eye socket.

wire the fragments directly with a no. 26 steel wire passed through drilled holes. Kirschner wire fixation is desirable and should be attempted first as it avoids facial scarring and the possibility of 7th nerve damage. In addition to Kirschner wires, a lower arch bar fastened to sound teeth establishes another plane of fixation. Number 26 wires anchored to posterior molars and twisted together in front of the lower arch will provide similar support. Such fixation is often referred to as a Risdon arch (fig. 6, *bottom right*). Subcondylar fractures are best left untreated until the patient has improved enough for interdental wiring.

Dislocations of the zygoma may be reduced by inserting a hook through the skin of the cheek and elevating the bone into proper position. Occasional stubborn displacements will have to be exposed through an intraoral upper labia sulcus or external hair line incision. Transverse Kirschner wires drilled across the face into the opposite zygoma provide fixation which is considerably more dependable than antral packs.[4] Points of stability are the nasal septum and the opposite zygoma, and these two bones support the depressed side by cantilever action (fig. 3, *center left* and fig. 5). No other fixation is necessary. The wire is clipped flush with the skin and should be extracted in about nine or ten days. Comminuted fractures of the floor of the orbit and malar eminence have to be supported by an internal pack, but after this has been accomplished it is advisable to drill the pack with a transverse wire into the opposite zygoma (fig. 3, *center right*).

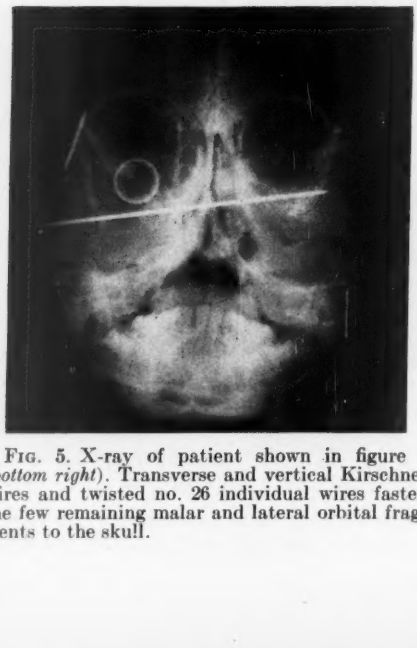

FIG. 5. X-ray of patient shown in figure 4 (*bottom right*). Transverse and vertical Kirschner wires and twisted no. 26 individual wires fasten the few remaining malar and lateral orbital fragments to the skull.

Multiple fractures of the orbital rim require perfect realignment because of their important role in extraocular movements and external appearance. Every fragment must be identified and oriented with respect to adjacent fragments, making internal reduction almost a necessity. Number 26 steel wires passed through drill holes fasten the fragments together until the complete ring has been restored (fig. 3, *top left and right and center left and right*). Compound fractures can usually be manipulated through existing soft tissue wounds. Incisions to expose closed fractures should be designed to fall into normal skin creases and should be placed horizontally at the base of the eyelids and laterally toward the hairline. Careful wound closure with fine, close sutures eliminates unsightly scarring. After the orbital rim has been restored circumferentially, horizontal stabilization is necessary to prevent unequal prominence of the malal eminences. Comminuted fractures in the floor of the orbit and disruption of the zygomatic arch allow forward or backward displacement of the entire orbital rim. Either reconstitution of the zygomatic arch by direct wiring or a Kirschner wire drilled into the opposite zygoma is necessary to prevent this deformity.

Fractures of the nasal bones should be accurately reduced as soon as possible and maintained with internal and external splints. Unstable fractures with avulsion of the inner canthal ligament must be reduced precisely and accurately fixed at the first opportunity or an important feature will be permanently lost. External splints, particularly in disoriented patients, cannot be trusted to maintain depth on the sides of the upper nose. Steel wires passed through the upper nose and tied over a padded metalic plate as described by Brown[4] are recommended for maintaining the relations of the canthal region (fig. 4, *bottom right*). The medial canthal ligament can be secured in its proper position by a pull-out wire tied over a button on the opposite side of the nose when the delicate crista lacrimalis or entire medial wall of the orbit is unstable.

In multiple fractures of several bones the mandible may be stabilized with Kirschner wires,

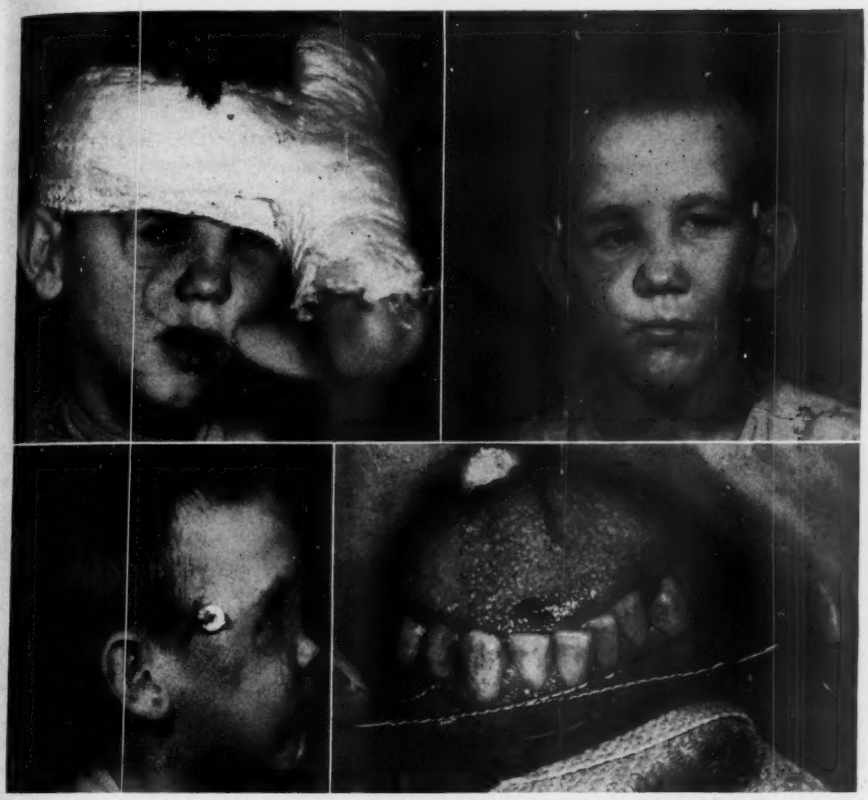

FIG. 6. *Top left,* subsequent arm to mouth lined flap serves to divide the nasal and oral cavities. The flap was carried through an existing scar in the left cheek and was divided in three weeks. *Top right,* six months after the accident, a superior labial sulcus was created by applying a skin lined conformer to a horseshoe-shaped surgical incision in the new palate. The conformer is stabilized in the sulcus by wires tied to buttons over each zygomatic arch. The right artificial eye had dropped into a low position following removal of the antral pack. There is no floor in the right orbit. *Bottom left,* lateral view shows prosthesis holding lower lip forward. A full denture will replace the plastic prosthesis after sulcus healing has occurred. *Bottom right,* Risdon arch, twisted no. 26 wires will be joined in the center to provide additional lower arch stability for mid-line fractures.

the upper jaw splinted against the mandible, both jaws stabilized to the malar bone which in turn may be secured to the angular process of the frontal bone. The fundamental principle encompassing all facial fractures in unconscious patients is to splint a fractured bone against the next higher stable bone, using internal direct methods of fixation rather than external splints or interdental apparatus.

POSTOPERATIVE CARE

The major objective in utilizing internal fixation is to reduce the need for elaborate postoperative care. The essence of postoperative care in patients with internally stabilized fractures is the establishment of a standard of cleanliness. External bandages should be small and changed as frequently as necessary. The oral and nasal cavities should be cleansed as often and as diligently as before surgery. A soft, child's toothbrush is useful in cleaning around arch bars and irregular dental surfaces. Male patients should be shaved each day and special attention afforded the entrance sites of Kirschner wires. These areas should be cleansed with a mild antiseptic and if the wires protrude, a tiny collodion dressing used to seal the area. Sutured wounds require gentle mechanical cleansing and

the removal of surface clots. A fine mesh grease gauze dressing will prevent the reaccumulation of blood and wound fluids.

In addition to the prevention of septic complications, supercleanliness is of special significance to the patient's family. Bloody dressings, matted beard, cracked lips and foul breath add immeasurably to the despair of frightened people who are facing a serious situation for the first time. Comfort and cleanliness are closely associated and a scrupulously clean patient, even though in deep coma, presents a reassuring appearance. Although most of the details of this sort of treatment are primarily nursing procedures, the standard of their performance will be set by the attitude of the physician in pointing out small details and rigidly enforcing the principles he has established.

SUMMARY AND CONCLUSIONS

1. Extensive soft tissue restorations and the reduction of facial fractures can be delayed safely for seven days if necessary.

2. Mandibular fractures are movable up to four weeks, but fractures of the nose, inner canthal region and maxilla become fixed after seven to nine days.

3. Coma, *per se*, is not a contraindication to general anesthesia as long as hypoxia is prevented. General anesthesia should be avoided, however, during the early undulating course of a severe brain injury.

4. Fractures are best stabilized by direct internal fixation rather than interdental wiring, projecting splints, headcaps or other external apparatus.

5. Pre- and postoperative care is centered around an adequate airway, good nutrition and strict standards of cleanliness.

Dept. of Surgery
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

REFERENCES

1. Benzer, P., and Schaffer, A. B.: The use of hyaluronidase in the treatment of traumatic swellings. Oral Surg., *5:* 1315, 1952.
2. Blinderman, J. J.: Control of edema, pain and trismus in oral surgery with an oral antihistamine. New York J. Den., *26:* 231, 1956.
3. Brown, J. B., and McDowell, F.: Internal wire fixation of jaw fractures, with note on external bar fixation. Surg., Gynec. & Obst., *75:* 361, 1942.
4. Brown, J. B., Fryer, M. P., and McDowell, F.: Internal wire-pin stabilization for middle third facial fractures. Surg., Gynec. & Obst., *93:* 676, 1951.
5. Wohlgemuth, P. R., and O'Brien, G. R.: Postoperative edema in maxillofacial surgery. Am. J. Surg., *94:* 537, 1957.

THE USE OF CARDIAC MONITORING SYSTEMS IN ANESTHESIA*

DAVID A. DAVIS, M.D., AND KENNETH SUGIOKA, M.D.

Chapel Hill, North Carolina

Recent years have seen the introduction of numerous electronic devices reputed to "monitor" cardiac activity, to "warn" the anesthetist of impending cardiac arrest and even to treat cardiac arrest should this catastrophe occur. Some of these devices have been introduced to the accompaniment of advertising material which may give a false sense of security to the user of these remarkable inventions. This advertising would lead one to believe that as long as the light shines or the bell rings or the needle moves, the cardiac action is satisfactory. More elaborate electronic instruments display the electrocardiogram continously on the screen of an oscilloscope or provide a continuous tracing on paper. Some provide the observer with a constant display of pulse rate. The combinations are infinite and probably the next few years will see electronic mechanisms of some descriptions in use in most operating rooms.

To discourage the use of these "gadgets" is not all the object of this discussion. These are remarkable instruments and are capable of giving the anesthetist valuable information. But to rely on instruments without recognizing what they are and their limitations is to court disaster. Basically all cardiac monitoring systems are electronic amplifiers. They receive a signal, amplify this signal and convert it into a sound, a flashing light, a deflection of a cathode ray beam or into something which can be seen, heard or even felt by the anesthetist. Most of these amplifiers use as a signal source the large R wave of the electrical activity of the heart—a signal approximating one millivolt (0.001 volt) in strength. A few amplifiers are sufficiently sensitive to detect the lower voltage signals of the P and T waves and because of voltage and frequency differences, convert these waves into sounds which can be distinguished from the larger R wave. But as amplifying systems, these cardiac monitors may be subject to the same disturbances which plague the television viewer, the radio fan or the high-fidelity enthusiast.

Just as a good antenna is necessary for good radio or television reception, a good connection between the patient and the electronic monitor is imperative. Although ordinary electrocardiograph electrodes may serve adequately for demonstration purposes, they are rarely satisfactory in the operating room, particularly if the patient is moved or is brushed against by the operating team. Then, too, changes in skin resistance or drying of electrode paste may cause distortion of the signal, creating a feeling of insecurity which is more confusing than informative. Recently a patient with Stokes-Adams syndrome was connected to a set of instruments designed to stimulate cardiac action by electrical impulses should spontaneous cardiac action cease, even momentarily. Confident in the efficiency of these electronic marvels, the attending physician slept well but was confounded the next morning when the patient reported she had been unable to sleep because every time she moved she received a series of painful shocks to her chest wall.

In our experience, ordinary hypodermic needles inserted just underneath the skin and taped firmly in place are much more satisfactory than surface electrodes. Even then passive movement of the patient may result in a signal which is more distracting than valuable. Imperceptible muscular activity, such as is encountered in hypothermia, may produce an artifact which is quite disturbing. On the other hand, the electrocardiograph or better yet, the electroencephalograph, may be invaluable in signaling the presence of this undesirable muscular activity.

"Static" is a frequent source of annoyance in the use of cardiac monitoring systems. It is imperative that the system be grounded well, a situation often lacking in operating rooms. Stray electrical signals from lights, elevators or any electrical equipment which is poorly shielded may produce signals which render monitoring equipment useless. Motor driven instruments used in orthopedic and skin grafting procedures render most monitoring systems useless when

* From the Department of Surgery (Anesthesiology), University of North Carolina School of Medicine and the North Carolina Memorial Hospital, Chapel Hill, North Carolina.

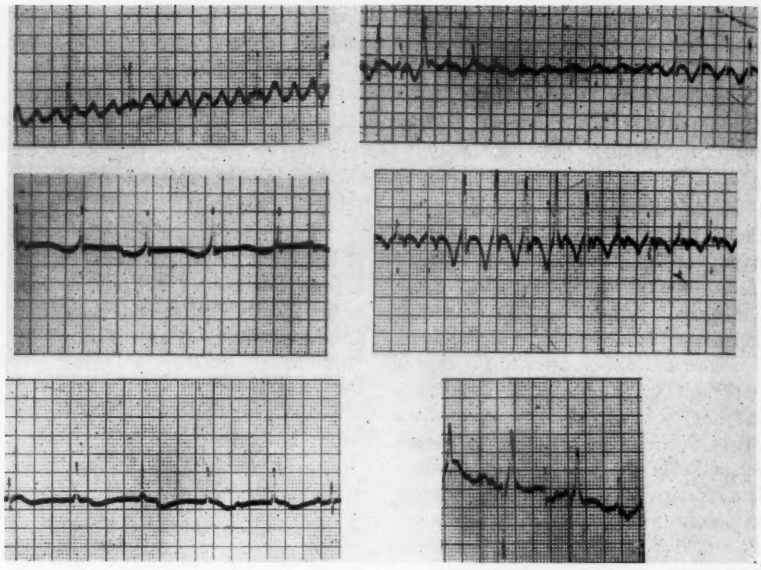

FIG. 1. Examples of cardiac arrhythmias not detectable by monitoring devices which depend on the R wave.

these instruments are employed. The electric cautery is a principal source of interference. Even when not in actual use, the presence of poorly shielded electrical equipment in the vicinity of the patient may result in disturbing interference. Monitoring apparatus often functions well at the beginning of an operation but becomes defective as metal surgical instruments come in contact with the body. This is simply the result of many antennae's picking up stray electrical impulses and placing them on the body surface which acts as a condenser. This situation is not uncommon, even in "modern" operating rooms, and is probably more frequent in the presence of x-ray instruments involved in cardiac catheterization and other procedures where cardiac monitoring is quite important. One instrument introduced recently* is quite useful in the presence of electrical interference. This instrument depends for its signal on the change in volume of a finger or toe which accompanies each peripheral pulse and, therefore, is free from electrical interference, even that produced by the electric cautery. This monitor, however, has certain disadvantages.

Placement of sensing electrodes may become rather critical. Since most monitoring devices depend on the electrical impulses produced by ventricular contraction, it is advantageous to place the sensing electrode in a position in which the amplitude of the R wave is maximal. The optimal location is over the precordium, with the indifferent electrode near the right arm for convenience. Next best is the lead II position of the electrocardiogram—right arm and left leg. Obviously the precordial position is denied during cardiac and certain other intrathoracic procedures, but even during operations in the abdomen or extremities one may find that the precordial monitoring system becomes ineffective during the inhalation phase of breathing. This is especially likely during assisted or controlled respiration and is due simply to the removal of the sensing electrode from the source of the electrical impulse—the heart. This can usually be corrected by changing the "volume control" or gain of the amplifier, but it is most disconcerting to have cardiac arrest signaled simply because the patient took, or was made to take, a deep breath.

Under certain circumstances the T wave may approximate the R wave in voltage. This may be relatively normal (lead III, low voltage) or abnormal (increased T wave in hyperkalemia),

* Allen Heart Monitor, Allen Electric & Equipment Co., Kalamazoo, Michigan.

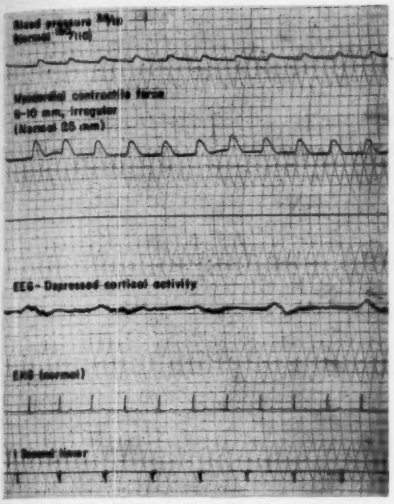

FIG. 2 Normal electrocardiogram in presence of severe and irreversible circulatory depression.

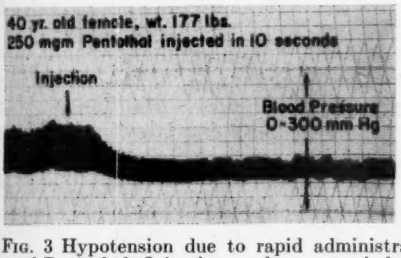

FIG. 3 Hypotension due to rapid administration of Pentothal. Injection made over period of 10 seconds; fall in blood pressure begins 4 seconds after completion of injection.

but some monitoring systems, being unable to distinguish between these waves, will signal each wave as it appears. This obviously leads to confusion which can be cleared by visualization of the entire electrocardiographic picture or even by the palpation of the peripheral pulse.

There are many changes in electrical activity of the heart which cannot be detected by monitoring systems which display only the R wave. Figure 1 illustrates some of these arrhythmias or cardiac abnormalities. Some of these are instantly detectable by cursory examination of the electrocardiogram, but how many surgeons or persons administering anesthetics are sufficiently versed in electrocardiography to detect them? Even if they are displayed adequately, will the average anesthetist recognize some of these abnormalities? Certainly not if he or she depends solely on the regularity of an electric signal.

The electrical voltage of the heart is only one of the criteria for the diagnosis of the presence or absence of severe cardiac disease. Cardiologists recognize the electrocardiogram as only one of the methods of diagnosis of cardiac disease. It is known generally that electrical activity of almost normal values can occur in the presence of ineffective circulation. Figure 2 shows a relatively normal electrocardiogram in the presence of almost no perceptible heart action. Certainly many cardiac monitors would interpret this picture as normal. To rely solely on such instruments is to court disaster.

Figure 3 illustrates the hypotension which accompanied the administration of a "little Pentothal" to a normal surgical patient. Figure 4 shows a profound hypotension accompanying the induction of anesthesia by a potent inhalation agent (chloroform) in a dog. The depression of myocardial contractile force and fall in blood pressure have reached dangerous levels even while the animal is still in the excitement stage. Every anesthetist will have little trouble visualizing in the background a surgeon complaining that induction of anesthesia is taking too long.

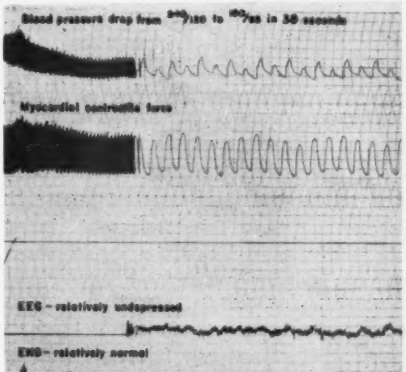

FIG. 4 Hypotension and myocardial depression accompanying rapid induction with chloroform (dog). Electroencephalogram shows very light anesthesia, and electrocardiogram shows little change except prolonged Q-T interval.

Under such circumstances cardiac monitoring systems may mislead anesthetists into killing patients. These devices monitor only one of the major functions of cardiac activity.

Again let it be emphasized that recently introduced cardiac monitors are not to be condemned. They are a useful and important adjunct in the estimation of a patient's welfare. But to trust entirely these electronic gadgets may endanger the life of the patient. The finger on the pulse and the blood pressure cuff still remain our most useful tools—the age of electronics has not rendered the skilled and attentive anesthetist obsolete. Of the systems available at present, the cathode ray oscillograph probably is the most valuable single instrument. Other instruments furnish important information, and may take some burden off the busy anesthetist, but there is still no satisfactory substitute for close observation of the anesthetized patient, using time-honored methods.

David A. Davis, M.D.
North Carolina Memorial Hospital
Chapel Hill, N. C.

THE ROLE OF NITROGEN MUSTARD IN THE PALLIATION OF MALIGNANT DISEASE WITH PARTICULAR REFERENCE TO PAIN*

JAMES F. NEWSOME, M.D.

Chapel Hill, North Carolina

Since 1946 when Rhoads[24] reported the previously classified data on the antitumor effect of methyl-*bis*-(β-chloroethyl)-amine hydrochloride (HN^2), various authors [2-8, 11, 12-17, 36-38] have reported their experiences with this agent in the palliation of neoplastic disease. The following is a summary of these reports:

The pharmacologic activity of nitrogen mustard is dependent upon the formation of a cyclic ethylenimonium derivative which is highly reactive, combining with various organic radicals of the amino acids, as well as prosthetic groups of various enzyme systems.[9, 10] More specifically, the cytotoxic activity apparently results from the interference with the synthesis of desoxyribose nucleic acid resulting in chromosomal aberrations and cellular death.[10] Theoretically then, and indeed in actuality, those cells with the greatest growth potential are most readily destroyed on contact with nitrogen mustard.

The toxic manifestations resulting from the clinical use of the nitrogen mustards are dependent upon their action on normal cells possessing a high mitotic rate, *i.e.*, bone marrow, mucosa of the gastrointestinal tract, the spermatogenic cells of the testes and embryonic cells of a developing fetus.[10] These general effects are responsible for the low therapeutic index of the mustards and make it imperative that the status of the bone marrow be known prior to the use of the alkylating agents. As would be expected, those patients with a normal bone marrow will tolerate higher doses than those with a damaged marrow as seen in many of the lymphomas.

Initially the dose scheme for the administration of the methyl-*bis* compound consisted of a total dose of 0.4 mg./kg. given intravenously in divided amounts over the course of two to four days.[11, 24] Without real experimental evidence, but more because of clinical impression,[15] the trend now is to give a full dose at one time. This method has resulted in no reported increase in complications. Karnofsky[13] has demonstrated that after dissolving nitrogen mustard in normal saline, 60 to 70 per cent of its activity is lost upon standing at room temperature for 15 minutes. This has led to the following method of administration.[13] An intravenous drip of sterile physiologic saline is started, using an 18-gauge needle in a suitable vein. After this has been securely placed, the desired amount of the agent is computed, mixed with sterile saline and immediately injected into the side of the intravenous tubing, following which approximately 100 cc. of saline are allowed to flow in as rapidly as possible. In a majority of patients there is the onset of nausea and vomiting of varying degrees of severity from 30 minutes to two hours following injection, and this usually lasts from one to four hours. The preinjection use of sedatives or antiemetics will temper this reaction considerably. In the author's experience, there has been no early severe postinjection complication resulting from this method as outlined.

In patients with normal bone marrows, a neutropenia, and to a lesser degree a thrombocytopenia, will be noted after about 10 to 14 days, lasting from 5 to 10 days with prompt recovery. There are, however, individual variations in the response to nitrogen mustard so that biweekly peripheral blood counts are imperative to appraise the sensitivity of the patient to the therapy and to institute prompt treatment should a severe neutropenia or thrombocytopenia develop.

Clinically the following results have been obtained:

1. Hodgkin's disease:[2, 4, 5, 7, 8, 11, 16, 30, 31, 36-38] For the localized lesion, x-ray is still the treatment of choice. With widespread, progressing disease, and in those lesions that have become refractory to roentgen therapy nitrogen mustard will give satisfactory remissions, lasting from three weeks to one year in 60 to 80 per cent of cases.

2. Malignant lymphoma (excluding the leu-

* From the Department of Surgery, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

This work supported in part by American Cancer Society Grant # T-IR88 a(T).

kemias):[2, 8, 11, 13, 18, 27, 34, 36, 37] Remissions can be expected in 30 to 60 per cent of cases. These have been in general more varied and are of shorter duration than those seen in Hodgkin's granuloma.

3. Bronchogenic carcinoma:[2, 3, 4, 12, 14-17, 22, 23, 26, 27, 29, 35] The most dramatic clinical responses are seen in those patients with vena caval or tracheal obstructions from the poorly differentiated lung carcinoma. The period of edema in the tumor bed, as seen following x-ray therapy, is not present with nitrogen mustard therapy. Karnofsky[15] has pointed out that x-ray following nitrogen mustard in lung cancer seems to lead to better remissions than the reverse of mustard after x-ray. Our experience in general agrees with this. Presently, the palliative treatment of bronchogenic carcinoma consists of one full dose of nitrogen mustard followed the next day with the first dose of the calculated amount of roentgen therapy.[15]

4. Miscellaneous cancers:[2, 4, 6, 25, 27, 29, 35, 36] Though experience with mustard has included a wide variety of lesions, except for the group mentioned above there have been no reports containing a sufficient number of patients to permit adequate appraisal. The results in carcinoma of the breast have been variously reported from 20 to 60 per cent remission without adequate description as to what constitutes a good remission.[29] It has been a consistent observation that the course of malignant melanoma is altered none at all by nitrogen mustard.[13, 16, 29] Experience in the palliation of gastrointestinal tract cancers with nitrogen mustard has likewise been too limited to allow evaluation.

For many of these lesions, the newer agents may hold more promise, *i.e.*, triethylenethiophosphoramide (thioTEPA) or triethylenephosphoramide (TEPA) for carcinoma of the breast,[19, 20, 29] carcinoma of the ovary[1, 21, 29, 33] and melanosarcoma,[28, 32, 33] but a discussion of these is beyond the scope of this report.

In spite of the paucity of reports dealing with these miscellaneous cancers, the distinct impression is obtained that many of these lesions may show good remission following mustard therapy. Cases 1 and 2 illustrate this point.

The random administration of nitrogen mustard to miscellaneous far advanced malignancies has frequently resulted in unexpected and gratifying remissions. It was noted that frequently in the absence of objective improvement there was a significant decrease in the severity of pain as well as an increase in the over-all sense of well being. This observation prompted a review of our patients treated with mustard with specific reference to the relief of pain as compared to objective benefit.

METHOD OF STUDY

The records of 148 patients with proved inoperable malignant disease were reviewed. Of this group, 81 records contained sufficient data to allow appraisal of the clinical response to nitrogen mustard. The remaining charts were those of patients receiving combination therapy and were therefore excluded. Of the 81, 49 records were found to contain a specific reference to changes in pain. The alteration in pain was further substantiated by noting the change, if any, in the type of analgesic and the frequency of administration as recorded on the doctor's order sheet or the nursing notes.

In a majority of cases the mustard was administered as Mustargen* according to the one dose method as described previously. Some of the patients were treated by the multiple dose method but their response in terms of relief of pain warranted inclusion in this report. Since this is not a study of dose method, these records were not excluded. Treatment was given as often as the bone marrow would permit, in some cases every three to four weeks. Peripheral blood counts obtained prior to the institution of therapy and continued at biweekly intervals revealed that no patient manifested a major complication. There were, however, two instances of local tissue damage from the extravasation of the agent at the injection site.

The results were divided into two major groups as shown in table 1, objective remission in terms of changes in size of palpable tumor masses and relief of pain. The relief of pain was graded from 0 to +++, 0 being no improvement, and +++, complete absence of pain or marked amelioration to the point of not requiring analgesics. The duration of remission was in general similar to that referred to before but was not otherwise tabulated. It was noted, however, that the duration of pain relief frequently outlived the effect of the agent on tumor growth.

* Merck and Company, Inc., Rahway, New Jersey.

TABLE 1

Response to use of nitrogen mustard in treatment of malignant disease

Disease	Objective Response*					Pain Response*				
	+++	++	+	0	Total	+++	++	+	0	Total
Respiratory										
Epidermoid carcinoma larynx			1		1			1		1
Epidermoid carcinoma bronchus	2	6	7	6	21	1	8	7	3	19
Adenocarcinoma bronchus				2	2				1	1
Gastrointestinal										
Epidermoid carcinoma tongue			1		1	1				1
Epidermoid carcinoma esophagus				1	1				1	1
Adenocarcinoma stomach	1		1	3	5		2			2
Adenocarcinoma colon	1		2	2	5	1		1		2
Lymphoid										
Hodgkins	9	7	1	1	18		4	3		7
Malignant lymphoma	3	4	1	3	11	1	2	1		4
Reticular cell sarcoma				1	1	1				1
Miscellaneous										
Anaplastic carcinoma		1	2	2	5	2	2		1	5
Mesothelioma			1		1	1				1
Carcinoma thymus			1		1				1	1
Melanosarcoma				3	3				1	1
Lymphoepithelioma		1			1					
Leiomyosarcoma				1	1					
Fibrosarcoma				1	1					
Carcinoma ovary				2	2				2	2
	16	19	18	28	81	8	18	13	10	49

*0 = no effect on rate of growth of tumor; + = questionable decrease or definite arrest of tumor growth; ++ = definite decrease in mass size without appearance of new lesions; +++ = marked decrease to absence of all overt evidence of the disease.

RESULTS

Objective remissions in the patients reported in this series (table 1) parallel in general the re-responses cited in the earlier portion of this paper. Except to point out that the greatest effects were noted in the patients with Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma, no detailed discussion of the objective results is necessary. As seen in the reports of other clinics, there were universally good remissions in those patients with severe vena caval obstruction from poorly differentiated lesions. Two additional patients have been treated since compilation of these data and achieved a grade 3 response. Case 3 is illustrative of this effect.

In the miscellaneous tumor group good responses were noted in many cases in which such would not have been predicted. As a result of this it has become our practice to treat every patient with extensive metastatic disease with mustard in the hope of achieving some palliation. We have been particularly pleased by the occasional excellent response in some of the cancere of the gastrointestinal tract. We are now in ths process of compiling data to clarify this point further.

Comparison of the two groups of data in table 1 reveals that the objective response and the relief of pain do not parallel one another. This fact is illustrated by the anaplastic carcinoma group and by the patient with recurrent carcinoma of the tongue (case 4). In the former, the objective response was rated as moderate in two patients, the majority showing no measurable improvement, yet there was dramatic relief of pain. In three of these patients who had previously required Demerol, there was complete disappearance of pain. Unfortunately, the follow-

up of these patients was not sufficient to permit an estimation of the duration of this relief. Two patients achieved a diminution in the intensity of their pain as evidenced by a change from Demerol to aspirin.

If one compares the ++ and +++ responses in each of the two groups of data, it is noted that 42 per cent of patients demonstrated measurable decrease in mass size, whereas 53 per cent achieved varying degrees of pain relief.

ILLUSTRATIVE CASE HISTORIES

Case 1. P. B., NCMH No. 02-32-37, was a 61-year-old Negro farmer who underwent partial gastric resection in October 1954 for adenocarcinoma with regional node involvement. Until February 1957 he continued his daily activities about the farm, at which time there was the onset of weight loss, anorexia and fatigability. He was readmitted in May 1957 with a 30-pound weight loss, and examination at this time revealed an 11- by 5- by 5-cm. firm, irregular, indurated mass about the umbilicus and a 3- by 3-cm. hard, nontender mass in the lateral angle of a right subcostal surgical scar. Except for a slight anemia the peripheral blood counts were normal. He was given nitrogen mustard, 0.4 mg./kg. intravenously in one dose, with slight nausea, and was discharged. One month later in the out-patient department he weighed 141 pounds, an increase of 20 pounds and reported that he had been working daily. The periumbilical mass measured 3- by 2- by 3-cm. and the right subcostal mass, 2- by 1-cm. He admitted to occasional discomfort in the abdomen but he had no other complaints. This remission lasted until the latter part of August 1957 when he returned with increasing weakness, further weight loss and an increase in the size of his masses. He received a second course of mustard therapy with less striking results. Since that time he has received without benefit two further courses of nitrogen mustard at monthly intervals. He was last seen in February 1958 at which time he was moribund.

Case 2. L. C., NCMH No. 05-65-39, a 44-year-old white female patient was first seen in May 1957, 5 years after undergoing total colectomy and an ileostomy for multiple polyps of the colon with malignant change and local invasion. Upon admission there was a 3- by 4-cm. ulcerated, bleeding lesion on the posterior vaginal wall, proved by biopsy to be adenocarcinoma of gastrointestinal origin; a firm, irregular, nontender mass deep in the right lower quadrant; and mild hepatomegaly. Following nitrogen mustard, 0.4 mg./kg. intravenously in a single dose, she was discharged and 4 months later returned to the out-patient department with moderate weakness, pain in the left hip and continuing bloody vaginal discharge. The vaginal lesion measured 2- by 2-cm. The mass in the right lower quadrant was still present but smaller. A second course of mustard therapy was given and in October her only complaint was of weakness. The pain had disappeared and the right lower quadrant mass was no longer palpable. In November 1957 the pain in her left hip returned, and a third course of mustard was given with only moderate relief. In January 1958 she was again admitted because of increase in bloody vaginal discharge and pain in her right hip. A fourth course of mustard was given and when last seen in February 1958 her pain had disappeared and the vaginal discharge was less but still present. Her weight continues to be stable and she is able to carry on a moderate amount of housework.

Case 3. M. F., NCMH No. 05-47-69, was a 66-year-old white man who in July 1957 was found to have a poorly differentiated bronchogenic carcinoma of the left upper lobe with supraclavicular node involvement and a left pleural effusion. During the next 3 weeks he received 68.4 mg. of thiotepa intravenously with relief of the pleural effusion, but weight loss, weakness and anorexia progressed. In July he was readmitted with respiratory distress, distended neck and arm veins, disorientation, cyanosis and edema about the face and neck. The tumor mass had increased in size, and there was now a Horner's syndrome on the left. A low tracheotomy was performed which netted some improvement in his breathing, but he continued to be stuporous and weak. After receiving nitrogen mustard, 0.4 mg./kg. in a single dose intravenously, there was marked improvement over the next 2 or 3 days as evidenced by a decrease in the size of the mass in the neck and improvement in his respiratory distress. The superior caval obstruction was relieved and except for a bout of left lower lobe pneumonia, he progressively improved until August 7, 1957, when he was discharged ambulatory. The tracheotomy tube had been removed 5 days previously. He expired at home on September 23, 1957.

Case 4. C. W., NCMH No. 04-73-67, was a 54-year-old white man who underwent a hemiglossectomy, hemimandibulectomy and a left radical neck dissection in August of 1956 for epidermoid carcinoma of the posterior one-third of the tongue. Recurrences at the operative site and in the left neck were noted in January 1957 for which he received radiation therapy with good results on each of three occasions. His fourth admission was in October 1957 because of severe pain along the distribution of the left maxillary branch of the

trigeminal nerve. At this time the tumor was found to be throughout the neck and in the base of the tongue with great difficulty in swallowing. Because of the pain and fear of further irradiation over an already damaged skin, he was considered a candidate for a prefrontal leukotomy. Before making this decision, however, intravenous nitrogen mustard, 0.4 mg./kg. in one dose, was given and was followed by marked relief of the pain, diminishing his analgesic requirement from Demerol to aspirin and occasional codeine. He was able to be at home until November 1957 when he was readmitted after a return of his pain of 3 days' duration. He again received nitrogen mustard therapy with relief, but not so dramatically as previously. He expired in December following hemorrhage from the left carotid artery.

DISCUSSION

It is difficult to make a true evaluation of the effect of nitrogen mustard on pain. The complaint of pain is prompted by many and varied stimuli which may in part be relieved by an attentive physician and the necessity of frequent follow-up visits for blood counts and appraisal of the effect of the agent on the tumor. Every physician is familiar with the general over-all improvement admitted by most patients when they feel "that something is being done." Every effort was made to disallow any such responses in evaluating the alteration in pain as reported here, although there was cognizance of the difficulty in achieving such objectivity.

The mechanism of pain relief by nitrogen mustard is not always apparent. Shrinkage of the tumor mass is an acceptable explanation when this mass is so situated as to produce stretching of nerve endings, to interfere with blood supply with developing ischemic change or to obstruct or distort the viscus. It would seem plausible that by minute, unmeasurable decreases in mass size there would result a decrease in tension or obstruction sufficient to reflect itself in subjective improvement which would be out of proportion to measurable objective benefit. Though nitrogen mustard is a powerful enzyme inhibitor, and in large doses a neurotoxin,[11] it seems unlikely that there is interference with the transmission of pain impulses.

The duration of pain relief in these cases ranged from two to eight weeks. As noted above, this in many cases exceeded the duration of objective response.

A striking feature following the use of nitrogen mustard intravenously has been the promptness with which the onset of remission is noted. The patient with superior caval obstruction will experience a noticeable improvement in respiratory distress in a matter of hours. The patient with severe pain usually will admit to some diminution in the severity of the discomfort on the morning following treatment. Changes in the size of the tumor mass, however, are delayed and are not usually apparent until the lapse of from seven to ten days.

It has been our custom to treat almost all patients with advanced malignancy with one course of intravenously administered nitrogen mustard as soon as it becomes apparent that the disease is progressing in spite of more conventional therapy and to repeat the agent as often as the bone marrow will permit. Though it has been recommended that mustard be given no more often than every six weeks,[13] we have repeated therapy at three- to four-week intervals without complication.

There are many patients who may well be treated as out-patients. For these we have been using rather large doses of Chlorambucil (an oral nitrogen mustard), giving in general the largest dose the bone marrow will tolerate and adjusting the dose accordingly. As with intravenous nitrogen mustard, there has been a significant relief of pain in many patients. This will be the subject of a future report.

SUMMARY AND CONCLUSIONS

The pertinent medical literature relating the clinical uses of nitrogen mustard and the experimental basis for this use has been presented. It is noted that in the 148 patients we have treated, mostly with one intravenous dose of the agent, that the objective remissions parallel those reported by others. Patients with Hodgkin's disease, malignant lymphoma (excluding the leukemias) or bronchogenic carcinoma (especially the poorly differentiated lesion with vena caval obstruction) show the best remissions. Many of the patients with supposedly "resistant" tumors may achieve a gratifying response following the use of nitrogen mustard.

In 49 patients an evaluation of the relief of pain was made, revealing that 53 per cent obtained a significant decrease in the severity as contrasted to 42 per cent objective remissions. It is suggested that nitrogen mustard has a definite place in the

control of cancer pain and should be considered for this purpose rather than purely for its antitumor effect.

Route 2
Chapel Hill, N. C.

REFERENCES

1. Anderson, M. C., Staley, C. J., Scanlon, E. F., and Preston, F. W.: Use of triethylene thiophosphoramide (thiotepa) in treatment of advanced cancer. A. M. A. Arch. Surg., *75:* 615, 1957.
2. Bierman, H. R.: Chemical agents in neoplastic disease. The evaluation of chemotherapeutic substance for clinical management. California Med., *78:* 44, 1953.
3. Boyland, E., Clegg, J. W., Koller, P. C., Rhoden, E., and Warwick, O. H.: The effects of chloroethylamines on tumors, with special reference to bronchogenic carcinoma. Brit. J. Cancer, *2:* 17, 1948.
4. Craver, L. F.: Nitrogen mustard: clinical use. Radiology, *50:* 486, 1948.
5. Dameshek, W., Weisfuse, L., and Stein, T.: Nitrogen mustard therapy in Hodgkin's disease. Analysis of fifty consecutive cases. Blood, *4:* 338, 1949.
6. Davis, W.: Some attempts at chemotherapy of cancer. Postgrad. M. J., *33:* 540, 1957.
7. Erf, L. A., and Bauer, R. D.: Clinical effect of nitrogen mustard on Hodgkin's disease. Am. J. Clin. Path., *19:* 372, 1949.
8. Gellhorn, A., and Jones, L. O.: Chemotherapy of malignant disease. Am. J. Med., *6:* 188, 1949.
9. Gilman, A., and Philips, F. S.: Biological actions and therapeutic applications of β-chloroethyl amines and sulfides. Science, *103:* 409, 1946.
10. Goodman, L. S., and Gilman, A.: *The Pharmacologic Basis of Therapeutics*, Ed. 2. The Macmillian Company, New York, 1955.
11. Goodman, L. S., Wintrobe, M. M., Dameshek, W., Goodman, M. J., Gilman, A., and McLennan, M. T.: Nitrogen mustard therapy. Use of methyl-bis-(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia, and other pathologic and miscellaneous disorders. J. A. M. A., *132:* 126, 1946.
12. Haddow, A.: The chemotherapy of cancer. Practitioner, *167:* 36, 1951.
13. Karnofsky, D. A.: Chemotherapy of neoplastic disease. New England J. Med., *239:* 299, 1948.
14. Karnofsky, D. A., Abelman, W. H., Craver, L. F., and Burchenal, J. H.: Use of nitrogen mustards in palliative treatment of carcinoma; with particular reference to bronchogenic carcinoma. Cancer, *1:* 634, 1948.
15. Karnofsky, D. A., Myers, W. P. L., and Philips, R.: Treatment of inoperable pulmonary cancer, primary and metastatic. Am. J. Surg., *89:* 526, 1955.
16. Leucutia, T.: Nitrogen mustard therapy. Am. J. Roentgenol. *61:* 104, 1949.
17. Lynch, J. P., Ware, P. F., and Gaensler, E. A.: Nitrogen mustard in the treatment of inoperable bronchogenic carcinoma. Surgery, *27:* 368, 1950.
18. Meyer, O. O.: Treatment of Hodgkin's disease and the lymphosarcomas. J. A. M. A., *154:* 114, 1954.
19. Moore, G. E.: Clinical experience with triethylenethiophosphoramide in the treatment of cancer with special reference to carcinoma of the breast. Roswell Park Bulletin, *2:* 31, 1957.
20. Moore, G. E., and Pickren, J. W.: Response of breast cancers to triethylenethiophosphoramide, pathological and clinical findings. A. M. A. Arch. Path., *65:* 98, 1958.
21. Naujoka, W., Crandel, C. E., and Treeter, W.: Experiences with triethylenethiophosphoramide (thiotepa) in advanced ovarian cancer. Bull. Sloan Hosp., *3:* 62, 1957.
22. Paterson, E.: Advances in the chemotherapy of malignant disease. Practitioner, *179:* 473, 1957.
23. Raphael, M., and Reilly, C. N.: The use of nitrogen mustard in advanced bronchogenic carcinoma. Dis. Chest, *25:* 210, 1954.
24. Rhoads, C. P.: Nitrogen mustards in treatment of neoplastic disease. J. A. M. A., *131:* 656, 1946.
25. Rollins, E., and Shaw, C. C.: ACTH and nitrogen mustard in the treatment of neoplastic disease. U. S. Armed Forces M. J., *6:* 1434, 1955.
26. Roswit, B.: Present studies of chemotherapy of bronchial cancer. Radiology, *69:* 499, 1957.
27. Scott, R. B.: The chemotherapy of malignant disease. Brit. M. J., *1:* 1, 1958.
28. Smart, M. C.: The use of thio-tepa (tirethylene thiophosphoramide) in melanotic sarcoma. Canad. M. A. J., *77:* 342, 1957.
29. Sykes, M. P., Phillips, F. S., and Karnofsky, D. A.: Comparative therapeutic activity of the nitrogen mustards and allied compounds. M. Clin. North America, *40:* 837, 1956.
30. Talbott, J. H.: Clinical manifestations of Hodgkin's disease. New York J. Med., *47:* 1883, 1947.
31. Tipton, E.: Nitrogen mustard in the treatment of Hodgkin's disease: a case report with remission. Texas Rep. Biol. & Med., *6:* 117, 1948.
32. Tullis, J. L.: Triethylene phosphoramide in the treatment of disseminated melanoma. J. A. M. A., *166:* 37, 4, 1958.
33. Ultmann, J. E., Hyman, G. A., Crandall, C., Naujoko, H., and Gellhorn, A.: Triethylenethiophosphoramide (thiotepa) in the treatment of neoplastic diseases. Cancer, *10:* 902, 1957.
34. Wallerstein, R. O., Aggeler, P. M., and Hoag, M. S.: Chemotherapy of leukemia and lymphoma. J. Am. M. Women's A., *12:* 417, 1957.
35. Whitehead, R. W.: Trends in chemotherapy of cancer. Postgrad. Med., *23:* 148, 1958.
36. Wintrobe, M. M., and Huguley, C. M., Jr.:

Nitrogen-mustard therapy for Hodgkin's disease, lymphosarcoma, leukemias, and other disorders. Cancer, 1: 357, 1948.

37. WINTROBE, M. M., HUGULEY, C. M., JR., MCLENNAN, M. T., AND LIMA, L. P. DE C.: Nitrogen mustard as therapeutic agent for Hodgkin's disease, lymphosarcoma and leukemia. Ann. Int. Med., *27:* 529, 1947.

38. ZANES, R. P., JR., DOAN, C. A., AND HOSTER, H. A.: Studies in Hodgkin's syndrome VII, nitrogen mustard therapy. J. Lab. & Clin. Med., *33:* 1002, 1948.

PATENT DUCTUS ARTERIOSUS—A DISCUSSION OF THE ABNORMAL PHYSIOLOGY*

RICHARD M. PETERS, M.D.

Chapel Hill, North Carolina

Patent ductus arteriosus is the most common congenital anomaly of heart and great vessels and the first such lesion to be cured by surgery. In the classical case the physical finding of a machinery-like continuous murmur is usually enough to establish the diagnosis. Although often in the early years of life the lesion may produce no symptoms and may be unsuspected for years, eventually the vast majority of people with this congenital defect develop cardiorespiratory embarrassment. In the uncomplicated case, therefore, since the operative mortality and morbidity are low, the diagnosis is considered reason enough to warrant surgical correction. However, in even the very young there may be complications with serious alterations in cardiovascular and pulmonary dynamics associated with this lesion.

It is the purpose of this paper to present a series of patients with patent ductus arteriosus to illustrate methods of study of the physiologic alterations, the clinical manifestations of these alterations and their treatment.

In the 5½ years since this hospital opened, 40 patients have been operated upon for patent ductus arteriosus. Table 1 gives the age distribution of these patients and the number with complications.

It can be seen that in the patients operated upon in the first 5 years of life the complication rate is very high. This is in large part due to the fact that we prefer to postpone operation until just before school age unless the patient is suffering some disability from the defect. In the older age groups the complication rate rises again as might be expected from the continued strain on the cardiovascular system.

Table 2 lists the types and incidence of major complications. To understand and discuss properly these problems both normal and abnormal physiologic factors must be reviewed.

In a normal adult the pulmonary artery pressure is 25/12 mm. Hg, and the pulmonary blood flow is equal to the systemic flow or approximately 3 L. a minute per square meter of body surface area at rest. In children the normal pressure has been reported to be somewhat lower 19/7.[7] These determinations are made by cardiac catheterization and in routine catheterizations most determinations of pressure and cardiac output are made at rest. However, some studies have been done[5, 8] during exercise in normal subjects and in patients with no emphysema or cardiac disease but with only one lung. From these studies Cournand[2] reached the conclusion that "the pulmonary artery pressure is maintained below the upper limit of normal until the flow exceeds approximately three times the basal flow." This is caused by an expansion of the vascular bed either by opening of new channels or widening of those already perfused, or a combination of both.

In patients with patent ductus arteriosus the direct communication between aorta and pulmonary artery results in a large flow from the systemic to pulmonary circulation. The amount of this flow depends upon the size of the ductus and the pressure differential between the aorta and pulmonary artery. Theoretically it would be possible to calculate the flow through the ductus if these entities were measured. However, it is not feasible to determine the size of the ductus and differential pressure. Since the blood leaving the right ventricle has a low oxygen saturation and the blood flowing from the aorta to the pulmonary artery has a high oxygen saturation, by determining these differences it is possible to calculate the proportion of the left heart output that is going through the patent ductus.

To make such a calculation the oxygen saturation of blood in a systemic artery, oxygen saturation of blood from the right ventricle near the pulmonary valve and the oxygen saturation of blood in the pulmonary artery must be determined. All of these samples can be readily obtained during cardiac catheterization. The blood in the pulmonary artery is a mixture of

* From the Department of Surgery, University of North Carolina School of Medicine and the North Carolina Memorial Hospital, Chapel Hill, North Carolina.

TABLE 1

Patients operated upon for patent ductus arteriosus

Patients	Age in Years					
	0-2	2-5	5-10	10-15	15-21	21-30
Total	3	8	10	6	8	5
With complications	3	5	1	1	1	3

TABLE 2

Major complications

Age	Cardiomegaly	Pulmonary Hypertension	Bacterial Endocarditis	Cardiac Failure	Below 3rd Percentile in Growth Curve
yr.	*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*
0-2	3/3	3/3	0/3	3/3	3/3
2-5	5/8	3/8	0/8	3/8	3/8
5-10	3/10	1/10	0/10	1/10	5/10
10-15	2/6	1/6	1/6	1/6	2/6
15-21	2/8	0/8	1/8	0/8	
21-30	2/5	1/5	2/5	0/5	

venous blood from the right ventricle and oxygenated blood from the aorta and so from the above values the amount of blood that flows through the lungs compared to that which goes to the systemic circulation can be calculated by the following formula:

$$\overline{Qpa} = \frac{SaO_2 - SvO_2}{SaO_2 - Spa\bar{O}_2}$$

$\overline{Qpa}$ = cc. of blood flowing through lungs/cc. flow to the systemic circulation;
SaO_2 = the systemic arterial O_2 saturation;
SvO_2 = the right ventricular O_2 saturation;
$Spa\bar{O}_2$ = the pulmonary artery O_2 saturation.

This formula is a modification of the formula of Comroe.[1] Table 3 lists the oxygen saturations in the pulmonary artery, right ventricle and aorta, the pressures in great vessels and $\overline{Qpa}$ or flow through the pulmonary artery per cc. flow to the systemic circulation. These examples are values from a 2½-year-old child with heart failure and pulmonary hypertension and another a 17-year-old boy who was found to have a patent ductus at a routine examination made of all basketball players. In the former the ductus was as large as the aorta, in the latter about 0.5 cm in diameter.

These patients demonstrate the effect of this flow on pressure and the resulting strain on the heart. In the basketball player the pulmonary artery pressures stay within normal range even during exercise. The shunt only increases his pulmonary artery flow at rest by 25 per cent. If Cournand is correct we can postulate that this boy's pulmonary blood flow does not become more than 3 times his systemic flow. In the 2½-year-old girl on the other hand her pulmonary artery flow at rest is at least 5.4 times her systemic flow. As a result of this fivefold increase in pulmonary flow she has pulmonary hypertension. Any increase in her activity which would require an increase in cardiac output will lead to even further elevation of the pulmonary artery pressure.

The clinical manifestations in these patients correlate well with anatomic size of the ductus and the physiologic derangements. The basketball player had a continuous murmur in the second interspace, no cardiac enlargement by either electrocardiograph or x-ray, questionable increase in the pulmonary vascular markings, normal systemic pulse pressure and had developed normally. His diagnosis was made on the basis of a continuous murmur. The 2½-year-old girl had right and left ventricular hypertrophy by x-ray examination, marked increase in the size of her main and peripheral pulmonary arteries, a systemic pulse pressure of 80 mm. of mercury, and retardation of growth.

The patent ductus had not handicapped the boy because the shunt was so small that he could compensate easily for the decrease in systemic flow and the increase in pulmonary artery flow. The second patient however was forced to lower her systemic flow thus leading to inactivity and underdevelopment. In spite of this she has developed cardiomegaly and pulmonary hypertension as a result of her large shunt.

The pulmonary vascular system operates best at a low pressure. If the pressure in the pulmonary capillary bed is raised above 30 mm. of Hg, the hydrostatic pressure tending to push fluid out of the capillaries will exceed the osmotic pressure of the plasma proteins and pulmonary edema will result. However, the effect of the high pulmonary artery pressure on the pulmonary capillaries can be diminished if the pulmonary arterioles contract. As a rule this occurs and as a result the pressure gradient from pulmonary artery to pulmonary capillary increases. At the same time, the elevation in pulmonary artery pressure dimin-

TABLE 3

Cardiac catheterization data

Age of Patient	O_2 Saturation			Pressure mm. Hg		$\frac{Q_{Pa}}{Q_{Sa}}$ or cc. in Pulmonary Artery /cc. in Systemic Circulation
	Right ventricle	Aorta	Pulmonary artery	Pulmonary artery	Aorta	
yr.						
2½ (Girl).....	56	94	87	55/25 M* 40	100/23	5.42
17 (Boy).....	69	92.5	74	25/6	158/66	1.25

* M = mean pressure.

ishes the pressure gradient across the ductus, with the result that less blood passes through the ductus. These two mechanisms then tend to aid the patient in compensating for his defect. Unfortunately they also lead to one of the most serious problems in the surgery of congenital heart disease to date; namely, fixed pulmonary hypertension.

In some patients with patent ductus or other left to right shunts the pulmonary arteries and arterioles become narrowed because of structural change until they offer so much resistance that the pulmonary artery pressure is equal to or greater than the aortic pressure. When this occurs the shunt is reversed. Blood flows from the pulmonary to the systemic circulation and cyanosis results. This cyanosis may be subclinical but if visible it is best seen in the feet or left arm because of the position of the ductus.

If the ductus is interrupted in patients with such reversed shunts, they are not helped and may not even survive the operative procedure. In such patients the normal distensibility of the pulmonary vascular bed has been destroyed by damage to the vessel walls. Any increase, therefore, in pulmonary blood flow is dependent on a rise in pressure. Acute rises in pressure in the pulmonary bed beyond the level of the systemic system can lead to acute right ventricular failure and death. If the ductus is still patent in patients with severe pulmonary hypertension and an increase in cardiac output occurs, the extra blood can be shunted through the ductus to the aorta and the acute rise in pulmonary artery pressure prevented. It is for this reason that patients with fixed pulmonary hypertension are better off with the shunt undisturbed.

This complication must be recognized in order to avoid a surgical hazard. One's suspicions should be aroused that fixed pulmonary hypertension is present in patients with the following findings: a change from a machinery type of murmur to one that is systolic as a result of an equalization of pressures during diastole, right ventricular hypertrophy, best demonstrated by the electrocardiogram, clear peripheral lung fields and cyanosis in feet and left arm, but these signs may not be conclusive and then the determination of *femoral* arterial oxygen saturation is essential. This should be done with the patient at rest, after exercising and when breathing 100 per cent oxygen. If there is incomplete saturation of the blood with oxygen under all of these circumstances, operative repair is clearly contraindicated. If only the sample following exercise and air breathing show desaturation further investigation is necessary. When a patient breathes 100 per cent oxygen the saturation should be greater than 100 per cent because in addition to the oxygen in combination with hemoglobin 2 volumes per cent of oxygen are dissolved in the plasma due to the fivefold increase in oxygen tension in the inspired air. The exact amount will vary with the method used for blood analysis. It is known that the inhalation of gas mixtures with low concentrations of oxygen lead to pulmonary arteriolar constriction and conversely in certain of these patients oxygen inhalation lowers the pulmonary artery resistance.[6] In patients whose oxygen saturation rises to normal breathing 100 per cent oxygen one may be hopeful that the pulmonary artery narrowing is partly due to spasm. In these cases cardiac catheterization should be done to see if there is some left to right as well as right to left shunt. If the latter is still large the result may be satisfactory.

In questionable patients an exploratory operation will be necessary. The ductus is isolated and pressures in the pulmonary artery and aorta recorded during a control period and then following occlusion of the ductus. In patients with fixed hypertension the pulmonary artery pressure in-

creases and the aortic pressure falls when the ductus is occluded. This is illustrated in the findings given in table 4 on 3 patients: an asymptomatic boy, 18 years old, a 10-year-old girl with pulmonary artery pressure greater than aortic pressure and a 3-year-old girl with pulmonary hypertension but no fixed shunt. In the boy ligation of the ductus only lowered the diastolic pressure in pulmonary artery and raised the systemic pressure moderately. The 3-year-old girl had a significant fall in the pulmonary artery pressure and a rise in aortic pressure. The 10-year-old girl, however, had a further rise in pulmonary artery pressure and a fall in aortic pressure. If this ductus had been tied this child would have developed right ventricular failure and have succumbed.

These are the physiologic alterations which can be measured and interpreted in patients with patent ductus arteriosus. They fail to explain satisfactorily why some patients develop fixed hypertension and others do not. Certainly the incidence is higher in patients with the largest ductus but the time course of development varies markedly. Attempts to relate the anatomic changes either to flow or to pressure have been inconclusive. Recently we have demonstrated elevation in left auricular pressure in these patients, which is promptly corrected with closure of the ductus. These findings will be reported in detail elsewhere. They may be an important factor in elucidating this problem.

The conclusion might be drawn from this discussion that the patient with an asymptomatic ductus need not be operated upon. Since the operative mortality in a large series[4] is less than one-half of one per cent and reference to table 2 shows the high incidence of late complications in untreated patients, this course is obviously erroneous. If the patients escape the problems of pulmonary hypertension and the resultant cardiomegaly, they frequently fall victim to bacterial endarteritis. It is interesting that two of our patients with bacterial endarteritis had had the diagnosis made one year before and refused operative repair because of a paucity of symptoms. The diagnosis of bacterial endarteritis may be hard to establish from blood culture because the bacteria may be filtered out by the pulmonary circulation. Anatomically the first vegetations are not in the ductus but on the pulmonary artery opposite the jet from the aorta. This has clinical significance because prompt antibiotic treatment prevents scarring about the ductus and makes operative repair easier after infection.

Finally it is important to relate these laboratory studies with the clinical findings in a group of patients. It can be seen from table 5 that the patients with pronounced symptoms showed the greatest incidence of abnormal findings on the electrocardiogram and with x-ray studies and if these are further analyzed the symptoms correlate with the degree of change. In the majority of patients with patent ductus arteriosus it is not necessary to measure the shunts and pressure. Unless definite cardiomegaly or significant symptoms are present operative care can be carried out simply on the basis of clinical findings. Only 10 to 20 per cent of children who have a patent ductus need these other studies. We have studied some of ours more extensively in the hope of elucidating some of the factors which cause pulmonary hypertension.

In most cases we have carried out ligation in continuity as recommended by Scott.[9] In those patients with large ductuses and pulmonary hypertension we have dissected out the distal

TABLE 4

Pressure changes recorded at operation

Age of Patient	O_2 Saturation, Femoral Artery	Pulmonary Pressure Artery Control	Pulmonary Artery Pressure, Post-occlusion	Aortic Pressure Control	Aortic Pressure, Postocclusion
yr.	*%*	*mm. Hg*	*mm. Hg*	*mm. Hg*	*mm. Hg*
3½ (Girl)*	92	50/35 M 42	34/18 M 23	94/60 M 80	100/85 M 92
10 (Girl)†	78	119/94	135/85	115/95	88/72
18 (Boy)‡	93	20/10	20/7	139/79	142/85

* Ductus as large as aorta.

† Fixed pulmonary hypertension-ductus large as aorta.

‡ Asymtomatic, small ductus.

TABLE 5

Summary of clinical findings

Age Group Symptoms	No. of Patients	Cardiac Size ECG*			X-ray Findings					Growth Failure	Cardiac Failure
		LVH†	RVH‡	Both	LVH	RVH	Both	Enlarged main PA§	Enlarged peripheral PA		
0–2											
Symptomatic	3	1	2	0			3	3	3	3	3
Asymptomatic											
2–5											
Symptomatic	4		4			1	3	4	3	3	2
Asymptomatic	4	1			2	0		1	1	0	0
5–10											
Symptomatic	3	1		1		1	1	2	1	1	2
Asymptomatic	7	1		1	1		1	2	2	3	
10–15											
Symptomatic	2	1		1			2	2	2	2	2
Asymptomatic	4				1			2	2		
15–20											
Symptomatic	1	1					1	1	1		1SBE¶
Asymptomatic	6						2	4	3		
21–30											
Symptomatic	2			1			2	1	2		2SBE
Asymptomatic	3				0	0	0	3	0	0	0

* ECG = Electrocardiogram.
† LVH = Left ventricular hypertrophy.
‡ RVH = Right ventricular hypertrophy.
§ PA = Pulmonary artery.
¶ SBE = Subacute bacterial endocarditis.

aortic arch and used a Potts-Smith clamp to occlude the aortic side of the ductus and Potts ductus clamp on the pulmonary side.[3] The ductus is then transected and sutured with a continuous mattress suture which is reversed as an end over suture. All of the patients in this series are clinically well at this time except for the one girl, who had fixed pulmonary hypertension. Many of the children have improved in their growth though some have not been followed long enough for this to be pronounced. Those children who had cardiomegaly at the time of operation do not have a prompt regression in heart size. However as they grow in size the heart does not grow as fast and they end up with a normal cardiothoracic ratio. The peripheral pulmonary vascular markings do return promptly to normal. The parents of many of the children have commented on the marked increase in physical activity postoperatively. To date no evidence of recanalization has been encountered.

SUMMARY

The majority of children who have patent ductus interrupted have no serious and permanent disability from this lesion. Correction before school age is advisable and a normal life expectancy can be anticipated. The mortality for this procedure in these uncomplicated cases is less than one per cent.

In this paper the physiologic abnormalities have been discussed. There is increase in pulmonary blood flow and if the ductus is large this can lead to pulmonary hypertension. If the pulmonary hypertension is not relieved, pulmonary vascular sclerosis can result in further elevation of the pulmonary artery pressure until the usual left to right shunt is reversed. These patients with pulmonary hypertension must be carefully studied to be certain closure of the ductus will aid them. Any patient with symptoms or evidence of cardiomegaly should have the ductus interrupted

at the earliest feasible date to prevent permanent damage to the pulmonary vascular bed.

Dept. of Surgery
University of North Carolina School of Medicine
Chapel Hill, North Carolina

REFERENCES

1. Comroe, J. H., Jr.: *The Lung: Clinical Physiology and Pulmonary Function Tests*, p. 187. The Yearbook Publishers, Inc., Chicago, 1955.
2. Cournand, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardio pulmonary diseases. Circulation, *2:* 641, 1950.
3. Freeman, N. E., Leeds, F. H., and Gardner, E.: A technique for division and suture of the patent ductus arteriosus in the older age group. Surgery, *26:* 103, 1949.
4. Gross, R. E.: The patent ductus arteriosus. Observations on diagnosis and therapy in 525 surgically treated cases. Am. J. Med., *12:* 472, 1952.
5. Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema, J. Clin. Invest., *27:* 10, 1948.
6. Kay, E. B., Sambhi, M. P., Nogueira, C., and Zimmerman, H. A.: The treatment of ventricular septal defects. J. A. M. A., *165:* 2168, 1957.
7. Kjellberg, S. R., Mannheimer, E., Rudhe, U., and Jonsson, B.: *Diagnosis of Congenital Heart Disease*, p. 90. The Year Book Publishers, Inc., Chicago, 1955.
8. Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A.: Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. Am. J. Physiol., *152:* 372, 1948.
9. Scott, H. W., Jr.: Closure of the patent ductus by suture ligation technique. Surg., Gynec. & Obst., *90:* 91, 1950.

ON THE USE OF AN ANTIHISTAMINE IN THE TREATMENT OF INTERSTITIAL CYSTITIS

JOHN L. SIMMONS, M.D., AND PAUL L. BUNCE, M.D.

In general the treatment of patients with interstitial cystitis is so unsatisfactory that any simple effective therapy is worth reporting.[3] This paper reviews our results in three patients treated with oral Pyribenzamine (tripelennamine hydrochloride). Although our series is small and the longest period of therapy has been only 18 months, the results have been so striking that this preliminary report seems justified.

The "rare type of bladder ulcer in women" as originally described by Hunner[6-8] in his papers of 1914 and 1918 was always associated with a sterile urine. Since that time, many investigators have found infected urine in their patients with Hunner's type of ulcer and the consensus now is that the urine may or may not be sterile.[4, 5, 9] Urine culture, therefore, seems to differentiate two varieties of this disease. This distinction is important because treatment will vary depending on the infecting organism. Two of our cases had sterile urine whereas one case was infected.

The subjective symptoms of frequency, nocturia and unusually severe bladder pain are out of proportion to the objective cystoscopic and urinary sediment findings. In the true Hunner's ulcer the urine is clear or contains only a few erythrocytes and leukocytes. In the infected cases the urinary findings are more marked. The cystoscopic findings in these two variants cannot be differentiated. The bladder capacity is small. Cystoscopy is frequently so painful the diagnosis may be missed unless the patient is examined under general anesthesia. The bladder mucosa appears edematous with scattered punctate areas of reddened mucosa and there may be small superficial ulcers which are not encrusted. This reaction is present only in the mobile portion of the bladder wall. With distention of the bladder the reddened areas may appear as granulation tissue, the ulcers may bleed, and occasionally the mucosa may split.

Pathologically, the inflammatory reaction extends through the entire thickness of the bladder wall and may go even beyond into the perivesical tissue and adjacent peritoneum. The diseased area is thickened and edema is a prominent feature. The overlying mucosa is thinned or absent in sites of ulceration. The submucosa is thickened and the area beneath the submucosa contains a heavy lymphocyte and plasma cell infiltration. Eosinophils are not conspicuous. Vascular and lymphatic channels are prominent throughout, and fibrosis and hyaline degeneration interrupt the muscle bundles.

The etiologic agent responsible for Hunner's ulcer has not been determined. When Hunner presented his cases, he felt that interstitial cystitis represented a lesion secondary to urethritis, which in turn was a result of metastatic infection from a distant localized focus.[7, 8] Faulty blood supply was implicated by Baumrucker[1] in 1955, when he produced a lesion in the dog resembling interstitial cystitis by ligating vessels of the posterior wall and vertex of the bladder. Powell[12, 13] made a strong case for the importance of lymphatic obstruction. Others[2, 10, 11] have felt that intramural streptococci, staphylococci or colon bacilli might be the etiologic agents, but Smith[14] was unable to culture any organism from a patient of his in which the bladder wall was macerated in a culture medium. In this report we would like to present evidence that histamine release in the bladder wall may play a dominant role.

CASE REPORTS

Case 1. L. B., a 62-year-old white female, was first admitted to North Carolina Memorial Hospital on March 18, 1956.

In 1948 she noted the sudden onset of heavy pressure in the perineal and suprapubic regions giving the sensation "that everything would burst out." This was accompanied by colicky suprapubic pain which radiated to her urethra, was brought on by the desire to void and relieved by urination. During this time she had frequency of 40 to 75 times per day and nocturia 5 to 10 times, passing small quantities of urine. She also began to void small clots of blood about every 3 months. She was first treated in 1949 by bladder dilations with marked improvement for about 4 months. Bladder fulgurations by another physician in 1950 relieved her symptoms for about 3 months. In 1952 fulguration again gave relief for 4 months. In the ensuing 3½ years she was treated for 2 years with Pro-Banthine and for 1 year with cortisone with no change in symptoms. She had had

4 episodes of hematuria in the 3½ years prior to admission.

The past history revealed the patient had undergone surgery for peptic ulcer in 1924. In 1948 she had had vague malaise and chills every other day for 2 weeks. A bullous type of skin eruption followed sulfa drug therapy. The menopause occurred 12 years prior to admission.

The only remarkable physical findings on admission were right costovertebral angle tenderness and right abdominal tenderness, most marked in the right lower quadrant.

The hemogram was normal and the blood urea nitrogen was 16 mg. per 100 ml. The routine urinalysis was within normal limits and the urine culture showed no growth at 48 hours. Chest x-ray and intravenous urogram were normal.

Cystoscopy revealed a 100-ml. bladder capacity. The lateral bladder walls had a granular appearance and submucosal hemorrhages appeared with distention of the bladder. Four days later, under general anesthesia, the bladder was dilated to a volume of 410 ml. and a 1 per cent silver nitrate solution instilled.

She did well temporarily but was readmitted 3 months later in June 1956, complaining of frequency of 25 to 30 times during the day and nocturia 2 to 15 times at night. Physical findings were unchanged but on this admission the unspun urine sediment had 8 to 10 erythrocytes and 2 to 4 leukocytes per high power field. Urine culture was again negative.

The cystoscopic findings revealed a superficial ulcer on the right lateral wall. The bladder was forcibly dilated to a volume of 540 ml. and silver nitrate instilled. Again she improved for a 6-week period but was readmitted 5 months later with a frequency of 25 to 50 times and 10 to 25 times nocturia. Physical examination and laboratory studies were as before. The urine culture was again sterile. The cystoscopic picture remained unchanged. On alternate days the bladder was dilated to 500-ml., 450-ml. and 500-ml. volumes. Silver nitrate was instilled each time. She was discharged from the hospital on Pyribenzamine, 50 mg. 3 times a day and Gantrisin for 2 weeks. At the time of hospital discharge she was advised to take: (1) Gantrisin for a 2-week period, and (2) Pyribenzamine t.i.d. indefinitely.

In the next 4 months she had nocturia on only 2 occasions and her frequency was only 3 to 4 times. Her abdominal discomfort had disappeared except for a lower abdominal pressure sensation after walking. One year after her last bladder dilation, in November 1957, she reported sustained improvement with frequency 4 to 5 times during the day and nocturia 1 to 3 times at night without urgency or dysuria. For 2 weeks during this interval she had noted hematuria with the passage of small clots accompanied by right lower quadrant discomfort. The bleeding stopped spontaneously, but lower abdominal discomfort is present for about 1 hour every 2 weeks. The findings at cystoscopy were essentially unchanged from the previous examination and the urine was still negative.

Case 2. C. R., a white male age 67, was first admitted to North Carolina Memorial Hospital in July of 1957. In 1953 he had undergone suprapubic prostatectomy elsewhere for symptoms of prostatism. His course was complicated by postoperative urinary tract infection requiring an indwelling catheter for a period of more than 6 weeks. In the first year after surgery he continued to have frequency every 15 to 30 minutes, nocturia 5 to 6 times and suprapubic pain. In 1954 he was explored through the original incision to "wash the infection out." Following this procedure he was told that "the sides of his bladder were hardened and would not stretch." His bladder symptoms continued. Four weeks prior to admission, in June 1957, he was unable to void and a 60- to 90-ml. residual was recovered by catheterization. An indwelling catheter remained until admission here.

On physical examination severe suprapubic tenderness with marked distress was the only pertinent finding. The hemogram and blood urea nitrogen were normal. The unspun urine sediment contained 6 to 10 leukocytes per high power field. Urine culture revealed *Aerobacter klebsiella*. Six acid fast urine cultures were negative. The intravenous urogram was normal except for a contracted bladder.

Under spinal anesthesia no residual urine was obtained at cystoscopy and it was possible to dilate the bladder to 200 ml. The vascular pattern of the bladder mucosa was prominent and there were several small ulcers which bled easily with bladder distention. Some of the ulcers were encrusted. After dilation 30 ml. of one-third per cent silver nitrate was left in the bladder. Following this procedure, he was discharged from the hospital on Pyribenzamine, 50 mgm. t.i.d., Pyridium, 0.1 gm. q.i.d. and Mandelamine, 0.5 gm. q.i.d.

One month later in August 1957, silver nitrate was again instilled in the bladder without distending it. From this point on his only medication was oral Pyribenzamine.

Case 2 was last seen in the clinic on April 10, 1958. He no longer has the suprapubic discomfort which formerly troubled him. He voids every 1 to 3 hours during the day with quantities up to 240 ml. About every 2 weeks he has a 2- to 3-day episode of having to void every 15 minutes with hesitancy, small stream and discomfort in the base and shaft of the penis. He will then void with a good stream and do well until another episode recurs. His urine sediment at this time is clear.

He was found to have only a 25-ml. bladder residual. In about 4 weeks he is to be readmitted to the hospital to see whether the overhanging anterior vesical neck noted 9 months ago could be the cause of the intermittent obstruction. He has taken no medication for his bladder except Pyribenzamine for 8 months.

Case 3. H. P., a 55-year-old white male was first seen at North Carolina Memorial Hospital in January 1958, complaining of intermittent flank pain, more severe on the right, of 18 months' duration. Bladder symptoms had become prominent for about 1 year and for the few months prior to admission he had frequency every 15 to 30 minutes, nocturia 4 to 5 times, urgency incontinence and enuresis.

On physical examination there was slight right costovertebral angle tenderness. The hemogram was normal. Leukocytes and many erythrocytes were present in the urine sediment. Routine urine cultures were negative as were acid fast cultures. The blood urea nitrogen was 27 mg. per 100 ml.

The intravenous urogram was interpreted as normal except for a small calculus in the left kidney. The cystometrogram showed extremely high pressures at small volumes; the bladder capacity was 200 ml.

Under general anesthesia his bladder would hold only 130 ml., and numerous areas of submucosal hemorrhage were noted on the vertex and lateral vesical walls. After cystoscopy the bladder symptoms and enuresis persisted. Three days later he was started on Pyribenzamine, 50 mg. q.i.d., and within 24 hours he had no more enuresis, nocturia only 2 times and frequency every 3 to 4 hours. Four days after starting Pyribenzamine cystoscopy under general anesthesia was again performed. This time the bladder capacity was found to be 340 ml. Numerous bleeding points were noted on the lateral walls. He was discharged from the hospital on Pyribenzamine, 50 mg. q.i.d.

DISCUSSION

A recent survey of interstitial cystitis by Bowers and Lattimer[3] lists some 35 methods of conservative treatment. Almost all of these involve repeated visits of the patient to the urologist's office either for parenteral injections, for bladder instillations, dilation, fulguration or for combinations of these procedures. Regional or general anesthesia is often required, and each posttreatment course may be most uncomfortable.

The treatment with Pyribenzamine is simple, safe, and in our limited experience seems to offer a most promising adjuvant in managing this disease. The first patient is a classical example of Hunner's ulcer. Her response to Pyribenzamine has been most dramatic and sustained. Previously she had derived only temporary benefit from bladder dilation, fulguration, Pro-Banthine and cortisone.

The second case we feel represents interstitial cystitis secondary to long continued urinary tract infection.

The third patient had such a dramatic response at a time when he was unaware of the therapy that he is included in this report even though we have only a short follow-up.

To explain the observed action of antihistamine in interstitial cystitis, it is necessary to postulate that histamine is present in the bladder wall and may be released there to act locally.

The origin of tissue histamine was not known until 1953 when Riley[14] demonstrated its presence in mast cells. This was further confirmed by Riley's work with West[15] in which the histamine value of various tissues was found to be proportional to mast cell content. To our knowledge the presence of mast cells in the human bladder wall

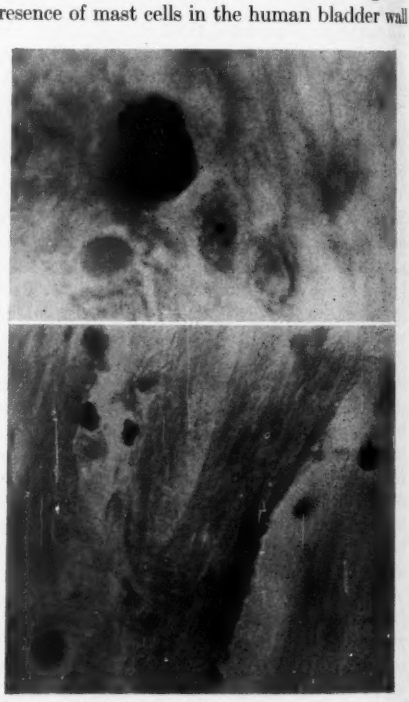

FIG. 1. (*Above*), a high power view of a mast cell in the bladder wall demonstrating course cytoplasmic granules surrounding a small nucleus. (*Below*), a less magnified section shows several mast cells scattered between the muscle bundles of the bladder wall.

has not been sought for previously. Normal bladder tissue taken at the time of segmental resection for bladder tumor was therefore examined specifically for these cells. Numerous mast cells were noted between the muscle bundles with fewer cells in the submucosa (fig. 1). From this we infer that the bladder wall has an appreciable histamine source although the mechanism of histamine release is not known.

Such a mechanism would explain the frequency of edema in the bladder mucosa as a result of numerous causes. That histamine release serves as the underlying cause of interstitial cystitis cannot be stated without further study and experiments are now underway to investigate this. The relief of this lesion by the use of antihistaminic substances, when other forms of treatment have failed, we consider highly significant.

SUMMARY

The lesion of interstitial cystitis resembles considerably a local histamine effect.

Mast cells, which produce histamine, have been shown to be present in the human bladder wall.

An antihistamine appears to be effective in the management of cases of interstitial cystitis.

The etiology of this disease remains obscure, but the response to antihistamines suggests that the local release of histamine may be one of the factors involved.

Dept. of Surgery
Division of Urology
North Carolina Memorial Hospital
Chapel Hill, N. C.

REFERENCES

1. Baumrucker, G. O.: An experimental study of the "elusive" bladder ulcer of Hunner. J. Internat. Coll. Surgeons, *23:* 221, 1955.
2. Bidgood, C. Y.: Tissue cultures in two cases of interstitial cystitis. Am. J. Surg., *4:* 140, 1928.
3. Bowers, J. E., and Lattimer, J. K.: Interstitial cystitis. Internat. Abstr. Surg., *105:* 313, 1957.
4. Cristol, D. S., Greene, L. F., and Thompson, G. J.: Interstitial cystitis of men. J. A. M. A., *126:* 825, 1944.
5. Hand, J. R. R.: Interstitial cystitis. J. Urol., *61:* 291, 1949.
6. Hunner, G. L.: A rare type of bladder ulcer in women: report of cases. Tr. South. Surg. & Gynec., *27:* 247, 1914.
7. Hunner, G. L.: Elusive ulcer of the bladder. Am. J. Obst., *78:* 374, 1918.
8. Hunner, G. L.: A rare type of bladder ulcer. J. A. M. A., *70:* 203, 1918.
9. Kretschmer, H. L.: Elusive ulcer of the bladder. J. Urol., *42:* 385, 1939.
10. Kretschmer, H. L.: Elusive ulcer of the bladder. Surg., Gynec. & Obst., *35:* 759, 1922.
11. Meisser, J. G., and Bumpus, H. C., Jr.: Focal infection in relation to submucous ulcer of the bladder and to cystitis. J. Urol., *6:* 285, 1921.
12. Powell, T. O.: Studies in lymphatics of the female urinary bladder. Surg., Gynec. & Obst., *78:* 605, 1944.
13. Powell, T. O.: Hunner ulcer; report of cases. West. J. Surg., *58:* 118, 1950.
14. Riley, J. F.: The effects of histamine liberators on the mast cells of the rat. J. Path & Bact., *65:* 471, 1953.
15. Riley, J. F., and West, G. B.: The presence of histamine in tissue mast cells. J. Physiol., *120:* 528, 1953.
16. Smith, G. S.: Interstitial cystitis. J. Urol., *67:* 903, 1952.

DR. KAORU SHIMA—HIS RECOLLECTIONS OF HIROSHIMA AFTER THE A-BOMB*

WARNER WELLS, M.D.†

Chapel Hill, North Carolina

Dr. Kaoru Shima is a prominent surgeon and civic leader in Hiroshima whose paternal forebears for five generations were physicians in Hiroshima prefecture. Educated at Osaka Imperial University, Dr. Shima did postgraduate study in Japan and completed his medical education in Austria, Germany and America. Here, the Mayo Clinic so impressed Dr. Shima that, upon his return to Japan, he incorporated many of its features in his own hospital. Dr. Shima's hospital was directly beneath the hypocenter when the first atom bomb in history was dropped over Hiroshima on the morning of August 6, 1945.

DR. SHIMA'S STORY

Chapter 1

I was a loyal, patriotic Japanese citizen. Win or lose I was dedicated to the conscientious execution of duties entrusted me as a doctor and as a civic minded resident of Hiroshima. I was a member of the City Council during the war and at one time served as its chairman. I was vice-president of the Volunteer Fire Fighters and active in the Emergency Relief Organization and the Hiroshima Surgical Association.

My first wife died in April 1945, and three of our four children had been sent to live with their grandmother at Aki-Nakano, 15 miles up a mountain valley from Hiroshima. My oldest child, a son, was enrolled at a small primary school deep in the mountains of Hiroshima prefecture. After April 1945, almost all the children in Hiroshima were removed to a residence at least 30 miles from the city. British children, I am told, were sent as far as Canada or the United States of America for sanctuary.

I mention my family only to emphasize that my entire attention and energies could be concentrated on my country, my city, my hospital and my patients.

On July 31, 1945, I received a telephone call from a friend and earlier patron, Dr. Tokuji Ueda, who had a 16-bed hospital 43 kilometers north of Hiroshima beyond Miyoshi in the town of Mikawa. Three patients, one with cancer of the sigmoid colon, a second with cholelithiasis and a third with recurrent appendicitis, were in need of surgery, and Dr. Ueda asked if I could come up and operate on them.

I was reluctant to go because of my duties in the city. Besides, travel was difficult since none but official journeys were permitted.

On the other hand, Dr. Ueda had consistently befriended me since I returned from my Wanderjahr financially impoverished. During the lean years before I got established, his kindly request for surgical assistance netted me at least 300 yen ($150.00) a year, in those days not an inconsiderable sum. This money I shared with my widowed mother in gratitude for the sacrifices she made so I could study abroad.

So you see, I could hardly refuse Dr. Ueda's request, despite the war and my own duties, and more particularly because I was now affluent and no longer needful of his thoughtful patronage. Moreover, there was no one else he could call. Consequently, I asked Dr. Ueda if I could come up on the afternoon of Sunday, August 5, 1945, and be prepared to operate on the following morning. Receiving an affirmative answer, I had a week to make the necessary arrangements. My personal affairs I arranged without difficulty, but to get a ticket to Mikawa was another matter. I commented that only officials or persons

* From the University of North Carolina School of Medicine, Chapel Hill, North Carolina.

† Dr. Wells is translator-editor of Dr. Michihiko Hachiya's *Hiroshima Diary*, an international best seller, that has seen three separate printings in England and America, and translation into ten languages other than English and the original Japanese. Dr. Shima's story is one of many personal, eyewitness accounts Dr. Wells collected in Hiroshima while working with The Atomic Bomb Casualty Commission for use in giving wider perspective to *Hiroshima Diary*.

The bomb dropped over *Hiroshima* was obsolete even before it was exploded. With newer developments in weapons and delivery, Dr. Wells believes man has now achieved the capacity to destroy himself as a species. To him, civil defense for any country can no longer be considered, except in terms of inspired statesmanship.

with military permits could use the trains. Believing my mission to be worthy and the end justified any reasonable means, I asked Dr. M. Fujii, director of the Railway Hospital, if he could get me a ticket. He was most obliging despite the personal risk to himself, and before the day of my departure he procured on the black market tickets for me and Miss Tsuyako Matsuda, my nurse.

Sunday came, and at 4:00 P.M. Miss Matsuda and I boarded a Geibi line train for Miyoshi. I left with a heavy heart and many misgivings, despite the plans I had made to cover my absence. I had even reviewed emergency instructions with my staff because we were desperately worried over the likelihood of an air raid attack. We had agreed that if a raid did occur the patients should be evacuated northward along the branch of the Ota river which coursed near our hospital.

Dr. Fujii, who had procured our tickets, was in Miyoshi to meet us when we arrived and with him was an old Osaka classmate, Dr. Okazaki. I learned that Dr. Amano, director of the Hiroshima Communicable Disease Hospital, should have come up on the same train with us but had missed it. The next day Dr. Amano, his wife and all of his children were killed.

FIG. 1. The Shima Hospital after the bombing The entrance columns of reinforced concrete were driven into the ground.

FIG. 2. The Shima Hospital rebuilt, and as it appears today. It is a testament to Dr. Shima's skill and devotion to medicine.

Dr. Fujii, Dr. Okazaki and I found ourselves stranded for the night. Our plight was not an unpleasant one because Miyoshi is a beautiful little mountain resort famous for its aiyu, a delicious small mountain trout caught locally by cormorants. We had a party. Sake was unexpectedly plentiful with the result that we all became thoroughly relaxed and pleasantly intoxicated. Late in the night I was awakened by a sound of B-29's, which rendezvoused over the town, changed course, and headed toward the northern coast bordering the Japan sea. We had to get up before day in order to make a 6:00 train, and after an hour's ride we reached Mikawa. We found a car waiting for us, so in another few minutes we were at Dr. Ueda's hospital.

I examined the patients with Dr. Ueda, and confirmed their need for surgery. I scheduled the patient with cancer of the sigmoid colon first because I expected difficulty and wished to be fresh and free of fatigue if I ran into trouble. The case proved to be difficult. I could free the upper end of the lesion, but in trying to free the lower end I found dense, restricting adhesions and as I tried to dissect the tumor free I tore into a blood vessel and the patient suffered a severe hemorrhage. By the time I had controlled the bleeding, the patient's condition was so serious that I abandoned all effort to do a resection and compromised by doing a colostomy.

While I was changing for the next case the phone rang. The police station was calling to tell us that Hiroshima had been attacked and was completely destroyed! They wished to know if any of the hospital personnel could be spared to rush to the scene of the disaster.

When I heard this news you can scarcely imagine the remorse I felt for having left my city. What could I do? What should I do? An old adage came to mind: "In order to save the big worm it is all right to kill the small one."

I had no alternative but to return to my city. My chest tightened. I felt pain as though it had been pierced by a nail. I canceled the other two operations and paused long enough to see the patient I had just explored. The thought came to me that if he should die he would be spared the agony of a drawn-out existence.

Dr. Ueda provided us with all the emergency supplies that we could carry. We returned, Miss

Matsuda and I, to the railway station. There we encountered two Hiroshima policemen who had been assigned to Western Headquarters, only a short distance from my hospital. Anxiously, I quizzed them about conditions. They told me that bombs had been dropped only in the north part of the city so that my hospital, in the center of town, could be expected to have escaped damage. I breathed a little more easily.

We reached Miyoshi about 4:00 P.M. By then, burned and injured persons were already pouring into the town. They were stunned and bewildered, and when I asked for news of Hiroshima they could only answer: "Completely destroyed!"

Our policemen friends took issue and accused the patients of spreading false rumors. More injured people were encountered at the next station below Miyoshi and they gave us the same story.

"How many planes came over the city?" I asked.

"Only three," was the reply.

How could an entire city be destroyed by only three planes I asked myself. Impossible, I thought. Surely our informants must be exaggerating! I was relieved, and so were the policemen. Nevertheless, the nearer we approached Hiroshima the more wounded we saw. Trains loaded with badly burned and injured people passed us. Their number was so great, in fact, that the few civilian nurses from the Women's Volunteer Association who accompanied them could provide only token assistance. This spectacle dispelled any optimism I might have felt.

Chapter 2

The train was not permitted into Hiroshima, being forced to halt at Yaga, a village some 2 kilometers east of the city. This annoyed me because not only was I impatient to get home, but I had all the emergency supplies and the prospect of walking before me. I had two sterile packs, a kit of instruments and my own bag. Being unable to find any means of transportation, I was forced to leave everything but my bag in the care of a farmer near the Yaga station. We began our walk and, as we made our way, subdued and thoughtful, we were met by hundreds of people going the opposite way; not healthy persons but people badly burned or injured, bewildered, in pain and despair.

Still we could not see Hiroshima because between us and the city lay a hill, Iwahana, that effectively obstructed our view until we could round its lower end. Dusk was upon us; it was nearing 7:00 in the evening. At this hour the air is normally hazy and the horizons dim, but tonight distant outlines were abnormally obscure. We finally rounded Iwahana and Hiroshima came into view. The spectacle staggered me. Over the city as far as I could see lay a pall of smoke, while scattered fires, near and distant, leaped toward the sky.

We walked on.

I had visited Italy during my student days and had seen the ruins of Rome and Pompeii. Tonight I saw those ruins again before me, but stark, bare and devoid of life. This was Pompeii, I thought, as it must have looked to those who tried to flee its gates in 79 A.D. Thus did I think as I approached Hiroshima, a city of fire, dust, smoke, ashes and hot air.

Only a month before I had been called to Kure after that city had been devastated by a fire raid. The appearance of a burned city was therefore not new to me, but here something was different, and it was a little while before I could discover what the difference was. Around me were houses which had not been damaged by fire but set crazily on their foundations, their tile roofs distorted or gone. (Iwahana was later discovered to be 3500 meters from the hypocenter of the A-bomb explosion.) I looked for bomb craters near where things had been so violently disturbed, but there were none. My bewilderment increased.

The nearer we came to the city, the fewer pedestrians we saw. I presumed that the wounded had been evacuated.

My hospital was in the center of the city near the Aioi-bashi (the T-bridge) and the police headquarters not far distant. Our policemen friends still accompanied us and they were as anxious as Miss Matsuda and I to get to the Aioi-bashi by as short a route as possible. Smoldering fires, however, blocked our way.

"How can we get into the city?" I asked a passerby.

"Entrance is impossible!" he answered.

His reply required no emphasis to convince us, for just ahead the Hiroshima Station, a landmark in the northeastern periphery of the city, was in flames. Skirting the station and proceeding through smoldering ruins, we came to an opening,

the East Drill Field. It was by now quite dark and, except where there were fires to light our course, we were obliged to walk cautiously.

On the Drill Field we found many wounded, both soldiers and civilians. They were too badly hurt to minister to themselves or to each other. All begged for water. Had I stopped to help them, I would have never reached my hospital. Their cries pierced my heart as I passed them by. We approached the old Hiroshima castle, now in ruins, and turned south alongside the remains of the army barracks. Our eyes became better accommodated to the dark and flickering light and we could distinguish dead and dying all around us.

We passed the West Drill Field and came to Kamiya-cho, the principal intersection in Hiroshima. From this point it required but a few minutes to reach the Aioi-bashi and my hospital. There had been no need for my haste. My hospital was completely destroyed. Nothing remained!

I tried to go into the ruins, but the heat was too intense. I retraced my steps. Near the Aioi-bashi I found many badly wounded and on the grounds surrounding the Chamber of Commerce building many others. We stopped at the bridge to reconnoiter. There the policemen left us to follow the river in search of their headquarters. Miss Matsuda and I stopped to consider what we should do.

I walked to a slight elevation in front of the Chamber of Commerce building and shouted: "The director of the Shima Hospital is here! Take courage! I will do what I can to help you."

All around me heads raised slowly and weakly, like the heads of so many snakes. From these heads came faint pleas of: "Help me, help me."

All were naked.

I didn't know why they were naked. In the dark I couldn't see that they were horribly burned, but I could sense that they were mortally ill. I gave heart stimulants to all I could find. How many, I have no way of knowing. Everyone asked for water. I had no container and could find none so I used a towel from my bag. Back and forth I went from river to patient, squeezing water from the towel I had dipped in the river. The gratitude of these pitiful people was heartbreaking.

Across the river, directly opposite, lay the Honkawa School. From that direction a girl's voice could be heard plaintively calling for help. Throughout the night she called, and the sound of her beseeching cry drove me near to madness. But I could not leave so many to go to one. I shall never forget her voice! It haunts me to this day.

With what little I had I worked until late in the night. How late I do not know, perhaps 2 o'clock. Finally, emotionally and physically exhausted beyond endurance, I lay down among the patients. I cannot say how long I slept. It was more like a nightmare, punctuated by the cries of the poor girl across the river. Around 5 o'clock in the morning, the time of gray dawn in early August, I roused. Words cannot express my feelings nor my impressions. As far as I could see, all was in ruin. The concrete buildings which stood out among the ruins served to accent the destruction. All brick and wooden buildings were destroyed. Most of the patients whom I had tried to treat during the night were dead. Those who lived were too weak to move and they lay quietly. As far as I could tell, there were none uninjured in the center of Hiroshima except Miss Matsuda and I. It was too early and too hazy to discover if any other living creatures were nearby.

The ruins of Pompeii magnified many times, but without the gay colors or the beautiful women. Only flames and wounded people all about. Depressed and miserable, I could resolve only to carry on as best I could.

Chapter 3

Miss Matsuda was still asleep and I left her undisturbed.

As the light improved, I could see the Red Cross Hospital nearly a mile to the south. Nearer, but in the same direction, stood the City Hall and some smaller concrete buildings. The Sumitomo, Geibi, Chugoku and the Fukuya buildings were visible to the east. North and west along the Ota river nothing remained but the ruins of the Yokogawa station. Only in the southeast, 3 miles away, were houses visible. All else was rubble and smoking ruin.

Burnt-over prairie lay around me with the streets, like pictures I had seen of battlefields, littered with scorched and twisted tramcars, buckled rails, fallen wires and broken poles. Only a few weeks ago Kure and now my home—Hiroshima! Tears filled my eyes.

"Is this war?" I asked myself.

"Is this what we must endure for the sake of victory?"

"Yes," I replied to my thoughts. "Even if our city is reduced to ashes!"

I still had faith in the army and navy. Perhaps they could destroy New York as Hiroshima had been destroyed. But my duties were here with the wounded. My nurse awakened and, without breakfast, we resumed our efforts for those around us. People passed. Some came to look for sons, wives, husbands or friends. Some were slightly wounded survivors seeking food and water. Many were naked and all were dirty. Their appearance embarrassed me and I found myself dirtying my clothes so that I wouldn't appear conspicuous.

What we could do was soon done so we decided to go to the Red Cross Hospital to see what was going on there. All the way we encountered many dead, but few wounded. Black, scorched bodies filled the tramcars, and in a garden pool near the City Hall we found a mass of corpses, some of whom, by their attitude in death, seemed to have been trying to flee when death overtook them. We found only a few alive, but they were so near death as to be moribund. There was nothing I could do for them. A small group stood talking on the patio before the City Hall. One carried a cane and was dressed in a summer kimono (yukata).

The mayor was dead.

One of the group, a city official, recognized me and asked if I could save the life of a friend of his, a former city councilman, who lay beside the pool we had just passed. I saw the man, but there was nothing I could do. Badly burned, his face blue and swollen, he died.

Miss Matsuda and I walked on until we reached the Red Cross Hospital. Built of brick and reinforced concrete, this hospital, the largest and most modern in the city, had escaped destruction. Hundreds of wounded littered the grounds immediately around the hospital entrance. A few recognized me and begged for help, so it was a tedious and painful task to make my way through their ranks in search of Dr. Takeuchi, the director of the hospital. I found Dr. Takeuchi and discovered he had been wounded and was further incapacitated by a broken collar bone. He seemed glad to see me and asked if I would see some patients for him, the first of whom was Dr. Hotta, a former president of the Hiroshima Medical Association.

Dr. Hotta was lying in a small room on a straw mat. The floor was littered with debris and chunks of concrete which made it about as comfortable as a rocky river bed. Dr. Hotta was horribly burned and in great pain. His wife, also severely burned, lay next to him. Between them on a table lay a dead woman. When I entered the room, Dr. Hotta was trying to ease his pain by pulling himself up by the table. With all his suffering his mind was crystal-clear. His whole interest centered on trying to help those around him before the effects of his own injury made it impossible for him to continue. He died shortly after my visit and his wife two days later.

I recall seeing Dr. Sasaki treating the wounded. The stream of makeshift stretchers and pallets seemed endless. On one was an old friend, Lieutenant Colonel Horie. He recognized me and called out in great excitement: "Shima, how are my wounds? I do not want to die! I cannot die! I have so many things to do; I cannot die until the war is won!"

I examined the Colonel and found only a few glass-cut wounds on his head. Otherwise, except for being exceedingly dirty, he showed no evidence of injury. "With these wounds you will not die," I said. "Take courage, my friend! Keep a hold on yourself!"

These words I uttered with great confidence and my experience as a surgeon was at hand to support me. But I was wrong. Colonel Horie was removed to the Naval Hospital at Iwakuni where he died on the 10th of August, three days later. I am not ashamed of my prognosis. I knew nothing of "radiation sickness" at that time and, for that matter, do not remember having heard that term in my studies here or abroad. I continued to do what I could for the burned and injured until nightfall.

Chapter 4

Miss Matsuda and I excused ourselves and retraced our steps to the scene of our destroyed hospital. The streets along the way were still strewn with black, scorched bodies, but the heat from the smoldering ruins had abated, so we could walk about in the debris without being burned.

I had been proud of my hospital. It was the oldest brick building in Hiroshima with massive walls over one meter thick. I had derived some comfort from this fact in that I considered our hospital to be proof against air raid and my pa-

tients enjoyed this reassurance. Before I left for Miyoshi my last injunction during my rounds to both patients and staff was: "In case a bomb is dropped, even in the garden, have no fear, cover yourselves with blankets and stay away from the windows."

But now, as I approached the hospital to see if my patients or staff had left any indications as to what route they had taken to escape I could see plainly that the hospital, which I had thought to be so strong and sturdy, had collapsed like paper. Nothing remained except the two concrete pillars flanking the entrance. I searched through the ruins and could find no sign of my patients. Many people lay dead in the streets around the hospital, but I could identify only one person. Slumped against one of the entrance pillars was the charred body of a woman whose features bore a vague resemblance to my head nurse. Miss Matsuda examined the mouth of this dead woman because she recalled that a month earlier she had undergone some orthodontic correction for prognathism. She found unmistakable evidence of the dental plastic procedure and remarked: "This is the head nurse."

We walked sorrowfully through the ruins, thinking of how things had used to be. I stumbled on an aluminum case about two meters from the ruins and recognized it as the instrument case I had procured abroad during my study. The instruments for abdominal surgery I stored in this case. Evidently, this little case, on a shelf by a small window in the operating room, had been blown through the window by the force of the blast. The lid was sprung a little but the instruments had not been dislodged, nor were they destroyed. They were tarnished, but still usable. I had removed my books and charts to my home in Aki-Nakano and had prepared to do likewise with my instruments. They remained the only vestige of the Shima Hospital.

Chapter 5

Scraps of paper or bits of clothing often remain after a fire, but except for my instruments, there was nothing, nothing to give a clue to the whereabouts or fate of my patients. We had not thought to search the West Drill Field, so Miss Matsuda and I went there. This was an army parade field a few blocks to the North with an air raid shelter used by both civilians and soldiers. We found some friends and acquaintances, but not a one of my staff or patients, nor did we find anyone who could give us news of them. We did what we could to ease the suffering and returned to the ruins of my hospital.

All day the heat had been intense, the dust and smoke suffocating. Neither of us had eaten since noon of the day before so you can imagine how depressed and tired we were. Actually as tired and depressed as we were, we found something to raise our spirits. A charred piece of wood had been proped in the ruins on which was written the following: "Dr. Shima! Please come immediately to the rear of Asano Sentei Park!" I forgot my fatigue and hunger. "My patients have taken refuge in Asano Sentei Park!" I exclaimed to Miss Matsuda. "Let's go there as fast as we can!"

With a cry of joy she set out to follow, and we turned our steps along Sarugaku-Cho. My brother-in-law had a pediatric clinic on this street. I could only guess at the location of his establishment because it had been completely destroyed. All we saw were charred bones in the smoldering ashes.

Asano Park was about 1500 meters from my hospital in the northeast section of the city. Situated on the west bank of the Ota River, it had been one of the beauty spots in Hiroshima. In earlier days this park was a part of the palace gardens of the Asano family, the ruling daimios, or princes of Hiroshima province. After the Meiji Reform in 1868, the properties of the princes and war lords were seized by the central government, and the Asano Gardens became a public park. A beautiful pond graced the center of the park and between this and the entrance the gardens were quite formal, being laid out in the strict classic tradition. On the far side, between the pond and the river, the design was along natural lines with miniature fields, rice paddies, hills and bamboo thickets.

Asano Park had now become a place of refuge, although during the hours immediately after the air raid it, too, had been swept by fire and many who sought safety there were cremated, or drowned when they tried to escape the fire by jumping pell-mell into the pond or river. Now this park swarmed with people like myself, searching for friends and relatives or giving first aid to those more seriously hurt than themselves.

We skirted the pond, as we made our way toward the ruined park. Within the pond I discovered countless dead eels and carp floating with their white bellies uppermost. This I thought

strange because why should these creatures, who live in the muck and ooze at the bottom of the pond, have been killed. We encountered dead and wounded on all sides, but I saw no one I knew. I became impatient and shouted, "Nurses of the Shima Hospital, where are you?" No one answered so I called again. Some of the wounded recognized me and begged for help. This time I did not stop, so intent was I to find my people. Again and again I called until finally, from the far corner, a man's voice answered: "Here we are, here we are!"

Racing to the spot, I found my youngest sister and a strange man beside her. There was no one else. Glad as I was to find my sister, it must be confessed that I was disappointed to find no others. By way of identifying himself the man spoke to me: "Dr. Shima, my family and I were seeking refuge in the park and we met this young lady, ill and in need of help. She informed us that she was your sister and begged me to look for you. I put her off at first because the confusion was unbelievable and I doubted very seriously if you could be found. She continued her entreaties, and though she appeared to be growing weaker, I set out for your hospital. I marvel that you are here because when I saw the ruins of your hospital, I could not imagine your being alive. You can imagine then how happy and surprised we are to see you."

I expressed my sincere gratitude to this man for he not only paused in his flight with his family to care for my sister, but had even left them to try to find me. My sister was lying on a comforter someone had unselfishly surrendered to her, attired in a cotton dress that was so shredded and torn she might as well have been completely nude.

Superficial examination disclosed only small cuts and bruises, none of which appeared serious. But my sister was mortally ill. Her lips were purple, her skin ashen and her pulse rapid and almost imperceptible. The shadow of death was falling over her. I asked what had happened and in a weak voice she answered: "Early in the morning there was an air raid alarm, but nothing happened. The all clear sounded and I went to the nursery on the third floor of the clinic to do some cleaning. Without warning there was a tremendous explosion. I had a vague sensation of riding on an elevator and thought to myself, 'I will die this way.' The next thing I knew, I was standing on the ground, while around me lay the ruins of the clinic. I fled to the street, but how I survived I do not know. Everyone else was killed. These kind people brought me here and I can go no further."

"What happened to your husband and children?" I asked.

"Our older child is with mother at Aki-Nakano but the baby was with us at home. When the explosion occurred my husband and the baby were eating breakfast with the maid. Since they were on the first floor, I presumed they escaped because they were no where to be seen when I came to my senses." This was all my sister could say and this little was with great effort. In an hour she was dead. Heart stimulants and all of my feeble efforts to ease and comfort her were in vain.

There was nothing more to do but try to get my sister's body to my ancestoral home in Aki-Nakano. I asked Miss Matsuda to go to the family and bring help. She complied willingly and set out on foot for the 3 li, or 12 kilometer, journey. She stopped at Kaitaichi-Machi on the way to ask a friend who had a hand truck to come for the body.

The second night after the bombing had come Miss Matsuda disappeared into the darkness, dragging her tired legs. I was alone with my dead sister for company. I still knew no more about the whereabouts of my staff and patients than I did when I first returned to Hiroshima. Fatigue had so dulled my senses I could scarcely think, and I recall no emotion as I prepared to spend the night by my sister's body. Before sleep overtook me I recall noticing that there were no mosquitoes. This was strange because they were usually very numerous in the park at night. I could hear the croaking of frogs and thought this strange because why should they survive when the carp and eels were dead. At intervals swishing sounds and soft thuds occurred nearby. These eerie sounds, I discovered, were made by birds who, from time to time, lost their perch in the trees above and fell to the ground dead. The rustling of wings and feeble peeps from above continued until I fell asleep.

Chapter 6

I slept soundly once sleep possessed me so I did not awake until early morning when I heard my name being shouted. My brother-in-law, Professor Sumitani had come down from Aki-

Nakano with the party to get my sister's body. They had looked for me most of the night. I was relieved to see my brother-in-law and grateful that he had come. He had been teaching in the Hiroshima High School when the explosion occurred but was fortunately uninjured except for burns to both hands. I left him to return my sister's body, arrange for the funeral and cremation. I did not feel that I could leave Hiroshima then even though I knew there would be no one at the funeral except my mother, my sister's 11-year-old son and my brother-in-law. Even the priest would not be present. His services were needed here in the city.

After seeing them off, I ate a rice ball someone gave me and decided to visit the City Office. A first aid station had been set up at the office manned by a team of doctors and nurses from nearby Yamaguchi. Theirs was one of a number of first aid stations now in operation, in general staffed by doctors and nurses from neighboring cities. I worked with this group for part of the morning and then returned to my hospital. There was still no news of my people although there was a note from a classmate who had apparently discovered I was alive and had paused to congratulate me. From bits of news gathered from here and there I learned that a bomb of terrific destructive power had been dropped near my hospital. I could not believe it had killed all of my staff and patients and I expect this hope kept me going. Tonight I learned that Japan was the first recipient of a new type of bomb. For fear other bombs might be dropped in our general area the sanitary department of the Prefectural Office ordered all drugs and instruments removed from Saijo, a town about 30 kilometers north of Hiroshima, to Miya, an island in the Inland Sea about 20 kilometers west of Hiroshima. Doctors were ordered to remain on location unless otherwise instructed by the government. A further measure in Hiroshima City was a proclamation ordering all remaining hospitals to operate as emergency aid stations. Since most of the hospitals had been destroyed or badly damaged, the order did little to increase the amount of aid available to the wounded. I suggested to the Chief of the Sanitary Office that we open an emergency hospital in the center of the city to care for those who were too ill to be moved. He approved my suggestion and asked me to organize and direct the hospital.

We chose to use the remains of the Fukuro-Machi Primary School because it lay very near the center of the city and was a two story concrete building whose walls and roof were still intact. We were so poorly equipped our conversion to a hospital was in name only. It could hardly be dignified by that name. I was the only doctor and Miss Matsuda the only nurse.

We removed as much of the rubble as we could and found a few straw mats with which we covered a portion of the floor. Long before our preparations were complete the wounded began to pour in in such numbers that the mats appeared ludicrous. They could accommodate only a few and the vast majority, including people who were badly burned, had nowhere to lie except in the ashes on the bare floors. The majority of our patients as you might surmise had been burned by flash or fire or cut by flying fragments of glass, metal or tile.

By now many of the patients had developed diarrhea and since we did not know that the diarrhea was caused by radiation exposure, we assumed it was caused by infection.

Patients with total body burns we gave priority for the straw mats. Even so, they became dreadfully soiled with ashes and dirt for lack of dressings to cover the raw surfaces. Severe infection was inevitable; and since we had no antibiotics, death claimed a high toll. We evacuated all who could be moved as soon as first aid administrations were complete in order to make room for more critically ill people.

The Sanitary Department tried to isolate patients with diarrhea, but so widespread was this condition, the futility of the task was apparent to everyone. The Fukuya Department Store was designated as an isolation hospital and all those with serious diarrhea, particularly with bloody stools, were removed there.

One of our major problems was the disposal of the dead. There was no burial or cremation service available, so I arranged to have our dead cremated in a corner of the playground. Day and night one could smell the odor of burning flesh and watch the flickering fire of the funeral pyre, and one only had to look out at night to see countless other fires throughout the city, each representing a makeshift crematory. The spectacle was certainly not good for morale, but there was no alternative. We did try to preserve the ashes of each victim so that relatives could later

administer funeral rites and a decent burial, although this problem soon became insurmountable. We had no priest to help us so it became my duty to say a prayer for the soul of each person cremated.

Flies and mosquitoes were nonexistent for the first two days; thereafter they appeared in countless numbers. Wounds, at first reasonably clean, soon began to seethe and crawl with maggots.

Chapter 7

I have remarked that I was the only doctor and Miss Matsuda the only nurse in the Fukuro-Machi Primary School emergency hospital. Many people though did offer their help in preparing food, clothing and otherwise assisting. Willing as they were, they could not take the place of our doctors and nurses. I did have the help of Dr. Yoshida for a short time. He was president of the Hiroshima Medical Association. He was appointed my assistant, although being his junior our status should have been reversed. Dr. Yoshida was being punished. When the bomb exploded he fled the city. Shortly after the Kure raid, doctors had been ordered to remain in the city in event of attack. The fact that Dr. Yoshida returned as soon as the fires abated made no difference, he was penalized for having disobeyed a perfunctory order and was punished by being made my assistant. One could look at Dr. Yoshida and realize he was as sick as many of my patients. He was tired and profoundly weak and on his face was the look of death.

"Dr. Yoshida," I exclaimed, "You are tired! Even though you have been sent here to help me, you are in no condition to do so. Please lie down on this mat and rest. Besides, the patients here all require surgical care and you are an internist."

Dr. Yoshida would not listen to me, so I set him to work taking the patients' pulse. When he finished this, I insisted he go home, but he wouldn't listen. This doctor and good friend helped me bravely for several days until he was relieved and put in charge of the isolation hospital in the Fukuya Department Store. In less than a month he died with radiation sickness.

Another friend, Dr. Amano, director of the communicable disease hospital, died with radiation sickness.

During the time I ran the emergency hospital at Fukuro-Machi, I slept at the Yokogawa police station which occupied temporary quarters in the relatively undamaged concrete Trust Building. Each day I passed the ruins of my hospital to see if any messages had been left for me. I had borrowed a pencil at the police station and framed a notice which I displayed prominently on a board propped in the ruins of my hospital.

Notice

Nurses, patients and others connected with this hospital please write below your names and addresses. Signed: Dr. Shima

As the days passed there were no signatures except those of relatives of my staff and patients.

About a week after the bombing we were told over a radio communication that Hiroshima had been hit with "an atom bomb," something new in destructive power and unique in the deadliness of its radioactive rays. I began to lose hope that I should ever see any of my staff or patients again. It was clear to me that my hospital had stood near the center of the explosion. My thinking had changed since that morning in the little hospital at Kozan when I first learned that Hiroshima had been bombed. I had reasoned then that if it were necessary for Hiroshima to be destroyed in order that Japan might live, well and good; or as we say: "To kill the small worm to save the large one." Now, I felt different. What a tragedy so many lives had been lost, so many made to suffer. My hospital was gone and with it all I had known. Had I not by accident been away only my white bones would be left to show for me. It all seemed so useless and so senseless.

The need for the emergency hospital was over after about 10 days. During this time as far as I could tell I remained healthy and active, although I was sorely depressed by the dead and dying around me and frustrated because I could do so little. I had had several worried messages from my mother begging me to come home so with the dissolution of my makeshift hospital I decided to pay my mother a visit. She was delighted to see me and said so but startled me a little by her remark: "I am glad to see you are alive and well and happy that you have lost your big hospital. I hope that you will not return to Hiroshima and build again, but stay here with me." My mother was thinking of the life my father had led as a country doctor

and was hoping I would stay home to take his place. I did not argue with her because I knew more than ever before that my place was in Hiroshima.

Each day Miss Matsuda and I returned to Hiroshima and part of the time was spent around the Fukuro-Machi emergency hospital where survivors had begun to take up residence, and the rest of the time in the ruins of my own hospital. Families of patients came to talk and to ask if there were any bones they could take home for burial. I could tell these people only that I didn't know whose bones were whose and suggested they take a handful of dirt rather than bits of bones. Some 80 persons had died in the Shima Hospital.

By now a little progress was being made in cleaning up the city. In the early days soldiers had been ordered in flanking movements to look for bodies. Bodies buried in debris, however, were missed for many were now being discovered by the odor of decay or by work crews removing the rubble. Even two years later when I began to rebuild my hospital many bones were uncovered as the foundation was excavated.

Chapter 8

As a surgeon, I was familiar with most of the problems that came to my attention as a result of the atom bomb, namely; the cuts, the burns, fractures and visceral injuries. The effects of radiation exposure, however, were new to me and even after I learned that radiation symptoms might be expected, I did not know what to look for. Nor in my training nor from my teachers do I recall that radiation illness was ever discussed as a syndrome. Within two weeks though I learned from experience the characteristic features of this disease of modern man, this syndrome of civilization, to wit: epilation, petechiae, sore mouth, diarrhea and bloody stools. That most of the symptoms were caused by profound disturbance in the bone marrow I learned later. Had we been interested in the peripheral blood we had not the equipment nor the personnel to make a study.

We observed that those who had been near the center of the explosion developed symptoms early and usually died, whereas those at a greater distance had fewer and milder symptoms and usually recovered. Thus, the location of the patient early became an important prognostic consideration.

Hemorrhage into a body cavity or into the substance of an organ or viscera became an important diagnostic consideration to the surgeon, particularly if the bleeding occurred in the abdomen. Peritoneal hemorrhage was frequently mistaken for acute appendicitis or other abdominal emergency until its frequent association with radiation exposure became recognized. Under the conditions with which we had to work the risk of an exploratory operation on a patient with radiation sickness was extremely grave. Paralytic ileus was a frequent occurrence in patients who developed hemorrhage into the walls of the intestine. In those who suffered damage to the serosa adhesions developed quickly, and in some caused acute intestinal obstruction. Perforations were not infrequent and resembled the perforations seen in typhoid fever. If the resultant peritonitis was localized, the patient could often be saved by drainage, but few survived in whom the peritonitis was generalized. Extensive serosal damage was frequentiy observed in severely radiated patients and when infection occurred, it was diffuse rather than localized.

Even now, after six years have elapsed, I inquire of each patient who comes to me as a candidate for abdominal surgery if he experienced radiation sickness after the bombing. It has been my experience that adhesions are more common in these patients and their resistance to infection less. Fortunately, these patients are less often seen now than formerly.

Professor Tsuzuki* visited my emergency hospital one day and asked many questions about the patients. I told him all I could about those who had been exposed. I was interested in another group as well, a group, who, like myself, had come into Hiroshima immediately after the bombing, such as firefighters, rescue teams, doctors, nurses and work crews. What would be the effect on them of coming into and living in the ruins of a city rumored to be un-

* Dr. M. Tsuzuki, formerly a professor of surgery in Tokoyo Imperial University, was head of the Japanese Division of the Joint Commission for Investigation of Atomic Casualties. Dr. Tsuzuki was well qualified for the task. In 1924, while doing graduate work at the University of Pennsylvania, he called attention to the acute effects of total body radiation in the experimental animal and described in detail the acute radiation syndrome thus anticipating by 19 years the syndrome in man. See: Tsuzuki, M.: Experimental Studies on Biological Action of Hard Roentgen Rays. Am. J. Roentgenol., *10:* 134, 1926.

inhabitable for 75 years? As a citizen and member of the city council I felt it my duty to answer this question. I had spoken encouragingly to all who questioned me, and cited myself as one who had been in the city continuously since the day of the bombing without having suffered any ill effects. To be frank, I did develop joint pains and sore gums and my urine became very dark. I did not experience the easy fatigability so many complained of, perhaps because my general health had been excellent. One might surely question the symptoms I described, but since my white blood count was 2000 I do believe I suffered some residual radiation injury. Later, I discovered something else about myself. From my student days I had experienced periodic attacks of migraine, but since the ordeal in Hiroshima I am no longer bothered with headache. On the other hand, indigestion, which I attributed to hyperacidity, became worse after the bombing. These are statements of fact. Whether they bear any relation to radiation exposure I am not prepared to argue.

I wish we could have made a careful study of the nonexposed re-entrants, but our work with the sick and injured consumed all our time.

Chapter 9

Word reached us that the Emperor was going to make an important broadcast at noon on August 15, 1945. The time came. Japan had lost the war! The Emperor was obliged to accept unconditional surrender! I can remember with what heavy hearts we heard this news. A group of girl students who had come in to help with the noon meal were huddled together crying. I went out into the playground and just stood awhile blankly, unable to comprehend what I had heard and finally unable to hold back my tears. Everything had come to an end. Apprehension for the future alone remained. Now, when I think back on those miserable days, it seems like a bad dream, one to make hair stand on end.

The rumor spread that when the victorious forces landed they would come into the houses and rape the women. I advised my daughter to take her child and flee farther into the country. Others did likewise. Our fears were groundless. Houses were not plundered, and our women were not raped.

A month had passed since the bombing of Hiroshima and by now I had transferred my practice to my home in Aki-Nakano. My father had had a small surgery attached to his office, and so it was here that I set up and with the help of two nurses began to see patients and do private surgery again. We were there when the first American soldiers came through. I thought to myself, "Yesterday, the young nurses were afraid of the soldiers, but today, they are leaning from the window saying 'Hello!' to some soldiers in a jeep, smiling, and asking for chocolate." I was amused and wondered if our soldiers would have been as polite to women as these Americans, or whether a difference in culture would have caused them to act differently.

At the end of the war the blackouts stopped and the lights came on again. Peace had come, but was the peace a fortunate one? Homes and families had been destroyed. People from the cities had been forced to take refuge in the country or in small villages. Thousands of demobilized soldiers were returning from Manchuria, Korea, China and the southern countries. When my brother returned, my sister embraced him and said: "I am glad to see you safe!"

She was happy. But I really think what she said and what she thought only lasted that night. One day passed and then another. My brother and his wife stayed on in the crowded house and shared the meager food. Why did they not leave and make a home for themselves? Where was there to go? Where was there more food? This fight with no sound, with no clash of swords was strong in Japan. The love of Buddha and the love of Christ were absent. Could this be peace in the true sense? Facing the difficult days ahead, it occurred to me that whether it was today or in the old days, in the East or the West, whatever the individual philosophy, the one force that could be expected to work for a true peace was the love of a mother.

Time passed and conditions improved with aid coming in from America. I rebuilt my hospital from the ruins of the old one, above which the first atom bomb in history was exploded. My new hospital is dedicated to peace and to the care of those who are poor and in need.

Warner Wells, M.D.
704 E. Franklin Street
Chapel Hill, N. C.